09077712 Page 1 (241) 01/03/2003

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 28	Oct 21	EVENTLINE has been reloaded
NEWS 29	Oct 24	BEILSTEIN adds new search fields
NEWS 30	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 31	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS 32	Nov 18	DKILIT has been renamed APOLLIT
NEWS 33	Nov 25	More calculated properties added to REGISTRY
NEWS 34	Dec 02	TIBKAT will be removed from STN
NEWS 35	Dec 04	CSA files on STN
NEWS 36	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 37	Dec 17	TOXCENTER enhanced with additional content
NEWS 38	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 39	Dec 30	ISMEC no longer available

NEWS EXPRESS December 31 CURRENT WINDOWS VERSION IS V6.01a,
CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),

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                AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
 NEWS HOURS     STN Operating Hours Plus Help Desk Availability
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 NEWS PHONE     Direct Dial and Telecommunication Network Access to STN
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FILE 'HOME' ENTERED AT 14:17:40 ON 03 JAN 2003

=> FIL REGISTRY
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

FILE 'REGISTRY' ENTERED AT 14:17:51 ON 03 JAN 2003
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STRUCTURE FILE UPDATES:    2 JAN 2003  HIGHEST RN 478001-04-6
DICTIONARY FILE UPDATES:   2 JAN 2003  HIGHEST RN 478001-04-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09077712.str

L1      STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1              STR
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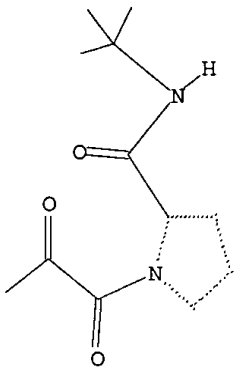

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SEARCH INITIATED 14:18:14 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     43 TO ITERATE

100.0% PROCESSED      43 ITERATIONS                          3 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          467 TO     1253
PROJECTED ANSWERS:               3 TO      163

L2             3 SEA SSS SAM L1

=> s l1 sss full
FULL SEARCH INITIATED 14:18:20 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   1032 TO ITERATE

100.0% PROCESSED    1032 ITERATIONS                       44 ANSWERS
SEARCH TIME: 00.00.01

L3            44 SEA SSS FUL L1

=> FIL CAPLUS
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              148.15     148.36

FILE 'CAPLUS' ENTERED AT 14:18:26 ON 03 JAN 2003
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FILE COVERS 1907 - 3 Jan 2003 VOL 138 ISS 2
FILE LAST UPDATED: 2 Jan 2003 (20030102/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

```
=> s l3
L4          12 L3

=> s l4 and HIV
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            79 HIVS
         47196 HIV
                (HIV OR HIVS)
L5          11 L4 AND HIV

=> d ibib abs hitstr l4 tot
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L4 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:676142 CAPLUS
DOCUMENT NUMBER: 137:197524
TITLE: HIV protease inhibitors and their use for treating HIV protease-associated diseases
INVENTOR(S): Wong, Chi-Huey
PATENT ASSIGNEE(S): The Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 153 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002068586	A2	20020906	WO 2002-US1695	20020122

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-262846P P 20010119
OTHER SOURCE(S): MARPAT 137:197524

AB With the help of X-ray structural analyses of drug-resistant HIV proteases and mol. modeling, a new type of inhibitor with a small P3 residue has been developed. These inhibitors are effective against HIV and its drug-resistant mutants, as well as FIV. Modification of existing HIV

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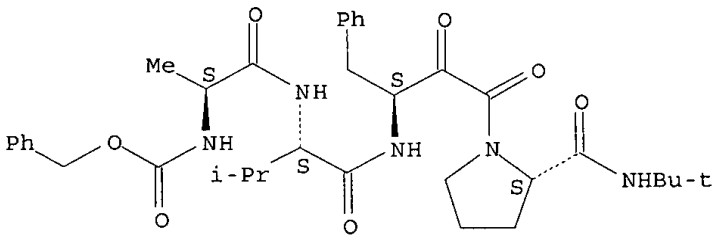
protease inhibitors by reducing the size of the P3 residue has the same effect. This finding provides a new strategy for the development of HIV protease inhibitors effective against the wild type and drug-resistant mutants and further supports that FIV protease is a useful model for drug-resistant HIV proteases, which often are developed through redn. in size of the binding region for the P3 group or the combined P3 and P1 groups. The HIV protease inhibitors may be used to treat diseases assocd. with HIV protease, e.g., AIDS.

IT **227317-37-5P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(HIV protease inhibitors and their use for treating HIV protease-assocd. diseases)

RN 227317-37-5 CAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-L-valyl-(.beta.S)-.beta.-amino-.alpha.-oxobenzenebutanoyl-N-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

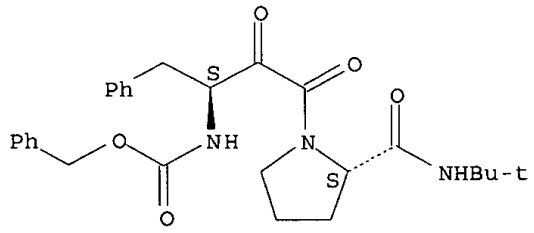


IT **141197-75-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(HIV protease inhibitors and their use for treating HIV protease-assocd. diseases)

RN 141197-75-3 CAPLUS

CN Carbamic acid, [(1S)-3-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:801933 CAPLUS
DOCUMENT NUMBER: 137:226
TITLE: A study on docking mode of HIV protease and their inhibitors

Golam Shameem

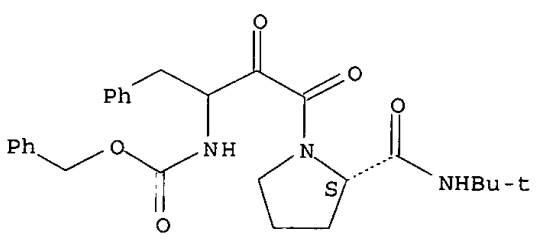
AUTHOR(S): Akaho, Eiichi; Morris, Garret; Goodsell, David; Wong, David; Olson, Arthur
CORPORATE SOURCE: Fac. Pharmacetuical Sci., Kobe Gakuin Univ., 518 Arise, Ikawadani-cho, Nishi-ku, Kobe, 651-2180, Japan
SOURCE: Journal of Chemical Software (2001), 7(3), 103-114
CODEN: CHSFEC; ISSN: 0918-0761
PUBLISHER: Kagaku Sofutowea Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The capability to propose feasible ways of binding a putative ligand inhibitor to a known receptor site is crucial to the successful structure-based drug design. A computer docking approach is to position or "dock" ligand and receptor mols. together in many different ways and then score each orientation by applying a reasonable evaluation function. AutoDock3.0 is an unbiased type docking program in which a user does not have to direct a ligand to an active site, but the system finds an optimal position after a ligand is placed in a random manner. Synthesized derivs. of the intact inhibitor (inh1) of HIV protease were investigated for their docking modes as compared with their Ki values. Among the derivs., inh3trans and inh6H were found to be more powerful inhibitors of HIV protease than the others. Gibbs free energy calcd. by applying mol. mechanics interaction energies was compared with the one obtained by using exptl. inhibitory potencies for a series of HIV protease inhibitors, and a fairly good correlation was found between the two. Based on this favorable correlationship between the computational and the exptl. results, the computational expts. were pursued for the compds. drawn by Sybyl taking into consideration the fact that unexploited carbon affinity regions (or hydrophobic regions) with sizable vol. were detected on the docking study of inh1 and inh8 against HIV protease. Those were compds. with a t-Bu substituted by various hydrophobic side chains. Among those a compd. with a benzyl group exhibited the lowest docking energy. Since one of the goals of this paper was to perform the computational drug-design expt. to investigate potential HIV protease inhibitors, the authors would like to leave the clin. investigational work for the expertise of those areas.

IT **191849-89-5 191850-28-9 191850-29-0**
433709-59-2 433709-64-9 433709-65-0
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(docking mode of HIV protease and their inhibitors)

RN 191849-89-5 CAPLUS
CN Carbamic acid, [3-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

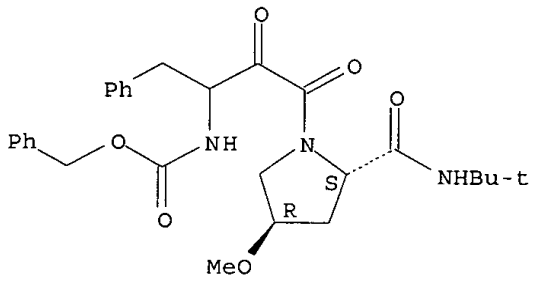
Absolute stereochemistry.



RN 191850-28-9 CAPLUS
CN Carbamic acid, [3-[(2S,4R)-2-[[(1,1-dimethylethyl)amino]carbonyl]-4-

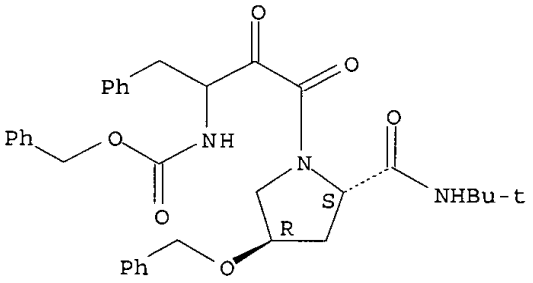
methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



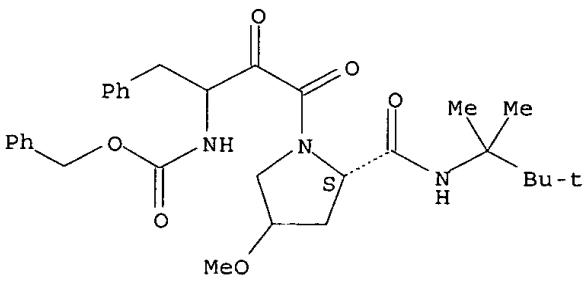
RN 191850-29-0 CAPLUS
CN Carbamic acid, [3-[(2S,4R)-2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 433709-59-2 CAPLUS
CN Carbamic acid, [3-[(2S)-4-methoxy-2-[[(1,1,2,2-tetramethylpropyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

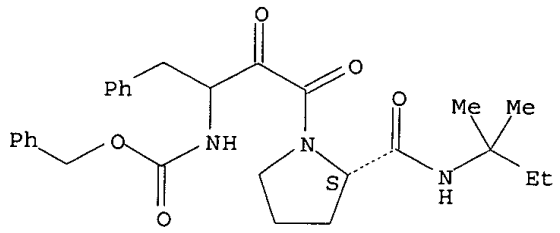
Absolute stereochemistry.



RN 433709-64-9 CAPLUS
CN Carbamic acid, [3-[(2S)-2-[[(1,1-dimethylpropyl)amino]carbonyl]-1-

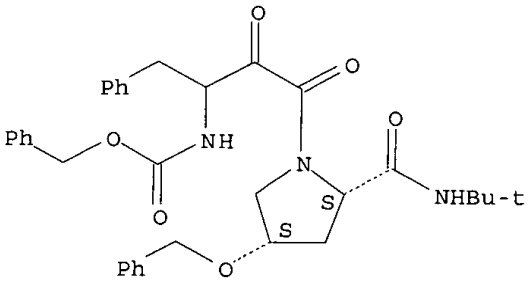
pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 433709-65-0 CAPLUS
CN Carbamic acid, [3-[(2S,4S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:390367 CAPLUS
DOCUMENT NUMBER: 131:45104
TITLE: HIV/FIV protease inhibitors having a small P3 residue
INVENTOR(S): Lee, Taekyu; Wong, Chi-Huey; Elder, John H.
PATENT ASSIGNEE(S): The Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9929311	A1	19990617	WO 1998-US25964	19981208

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9919045 A1 19990628 AU 1999-19045 19981208

EP 1039886 A1 20001004 EP 1998-963800 19981208

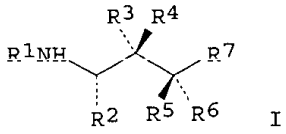
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.: US 1997-67959P P 19971208

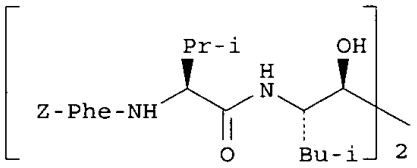
WO 1998-US25964 W 19981208

OTHER SOURCE(S): MARPAT 131:45104

GI



I



II

AB Protease inhibitors I [R1 = H, carbobenzyloxy (Z), Z-Val, Z-protected dipeptidyl; R2 = benzyl, isobutyl; R3, R4 H, H; H, OH, O; R5, R6 = H, H; O; R7 = prolinamide or N-tert-butylprolinamide residue] were prepd. Thus, peptidyl diol II was prepd. and showed Ki = 487 .+-. 20 and 5.5 .+-. 0.8 for inhibition of FIV PR and HIV PR, resp.

IT **141197-75-3P 227317-37-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HIV/FIV protease inhibitors having a small P3 residue)

RN 141197-75-3 CAPLUS

CN Carbamic acid, [(1S)-3-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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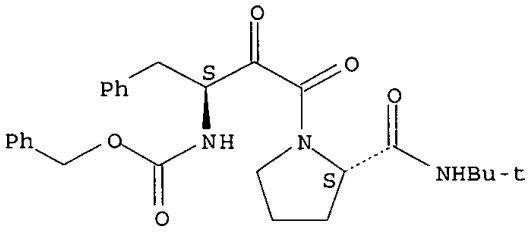
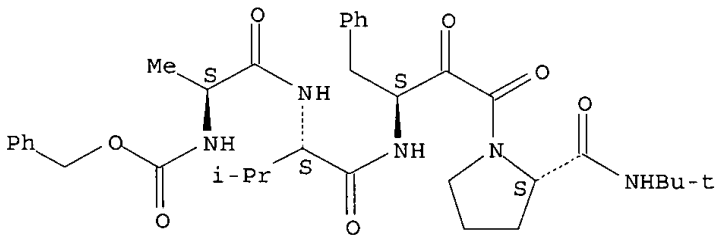


RN 227317-37-5 CAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-L-valyl-(.beta.S)-.beta.-amino-.alpha.-oxobenzenebutanoyl-N-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

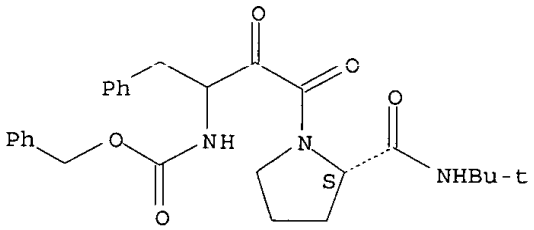
L4 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:73185 CAPLUS
DOCUMENT NUMBER: 130:276229
TITLE: Development of a New Type of Protease Inhibitors, Efficacious against FIV and HIV Variants
AUTHOR(S): Lee, Taekyu; Le, Van-Duc; Lim, Dongyeol; Lin, Ying-Chuan; Morris, Garrett M.; Wong, Andrew L.; Olson, Arthur J.; Elder, John H.; Wong, Chi-Huey
CORPORATE SOURCE: Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1999), 121(6), 1145-1155
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Based on the structural anal. of FIV protease and drug-resistant HIV proteases and mol. modeling, a new type of inhibitors with a small P3 residue has been developed. These inhibitors are effective against HIV and its drug-resistant mutants, as well as SIV and FIV. Modification of existing HIV protease inhibitors by reducing the size of the P3 residue has the same effect. This finding provides a new strategy for the development of HIV protease inhibitors effective against the wild-type and drug-resistant mutants. It further supports the use of FIV protease as a useful model for drug-resistant HIV proteases, which often have a more constricted binding region for the P3 group or the combined P3 and P1

groups.

IT **191849-89-5P 222849-01-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of a new type of protease inhibitors, efficacious against FIV and HIV variants)

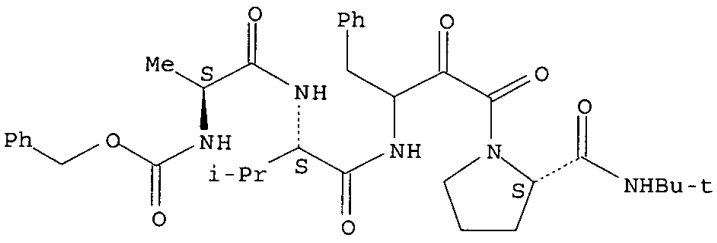
RN 191849-89-5 CAPLUS
CN Carbamic acid, [3-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 222849-01-6 CAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-L-alanyl-L-valyl-.beta.-amino-.alpha.-oxobenzenebutanoyl-N-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:473732 CAPLUS
DOCUMENT NUMBER: 127:81793
TITLE: Preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors
INVENTOR(S): Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
PATENT ASSIGNEE(S): Scripps Research Institute, USA; Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
SOURCE: PCT Int. Appl., 202 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

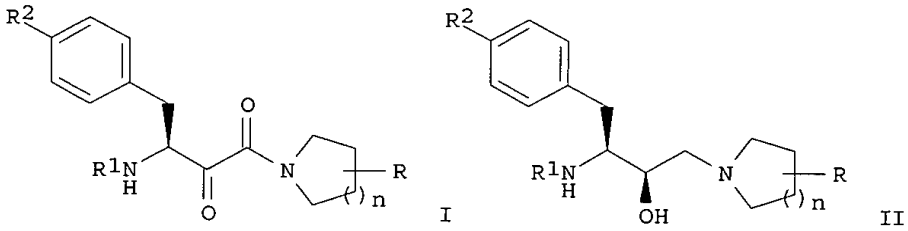
Golam Shameem

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9721100	A1	19970612	WO 1996-US19571	19961209
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2238337	AA	19970612	CA 1996-2238337	19961209
AU 9712844	A1	19970627	AU 1997-12844	19961209
AU 728373	B2	20010111		
EP 873519	A1	19981028	EP 1996-943657	19961209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2000502332	T2	20000229	JP 1997-521485	19961209

PRIORITY APPLN. INFO.: US 1995-568532 A2 19951207
WO 1996-US19571 W 19961209

OTHER SOURCE(S): MARPAT 127:81793

GI



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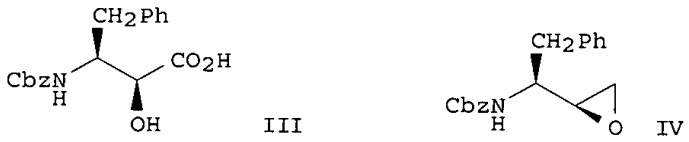


III IV

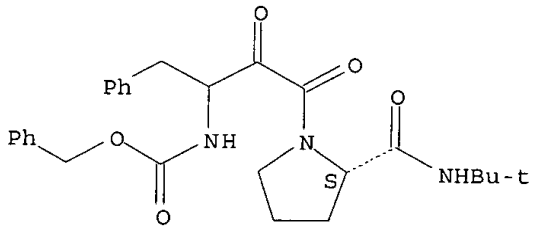
AB Combinatorial libraries of HIV and FIV protease inhibitors are characterized by .alpha.-keto amide or hydroxyethylamine core structures I and II [n = 1, 2; R = one or more groups CONHCMe3, CH2OH, CH2OMe, CH2OCH2Ph, OH, OCH2Ph, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy, etc.; R1 = PhCH2O2C (Cbz), Me3CO2C (Boc), acyl; R2 = H, HO, PhCH2O, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy] flanked by on one side by substituted pyrrolidines, piperidines, or azasugars and on the other side by Phe, Tyr, or substituted tyrosines. The libraries are synthesized via coupling of the nitrogen heterocycles with hydroxy acids, e.g. III, followed by oxidn. to the keto amide, or a one-step coupling with epoxides, e.g. IV. Highly efficacious drug candidates are identified by screening the libraries for

binding and inhibitory activity against both HIV and FIV protease. Drug candidates displaying clin. useful activity against both HIV and FIV protease are identified as being potentially resistive against a loss of inhibitory activity due to development of resistant strains of HIV.

IT **191849-89-5P 191850-27-8P 191850-28-9P**
191850-29-0P 191850-30-3P 191850-31-4P
191850-32-5P 191850-33-6P 191850-34-7P
191850-35-8P 191850-36-9P 191850-37-0P
191850-38-1P 191850-59-6P 191850-60-9P
191850-61-0P 191850-91-6P 191850-92-7P
191850-93-8P 191850-94-9P 191850-95-0P
191850-96-1P 191851-37-3P 191851-40-8P
191851-42-0P 191851-43-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

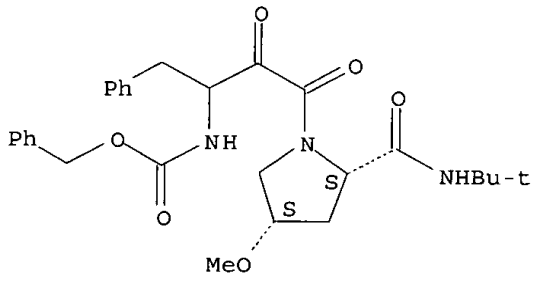
RN 191849-89-5 CAPLUS
CN Carbamic acid, [3-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191850-27-8 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,4.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

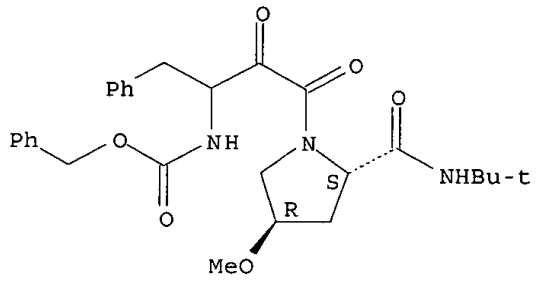
Absolute stereochemistry.



RN 191850-28-9 CAPLUS
CN Carbamic acid, [3-[(2S,4R)-2-[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

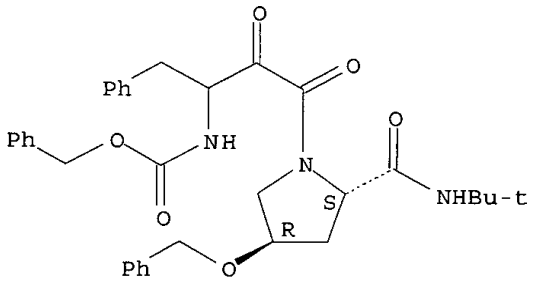
Golam Shameem

Absolute stereochemistry.



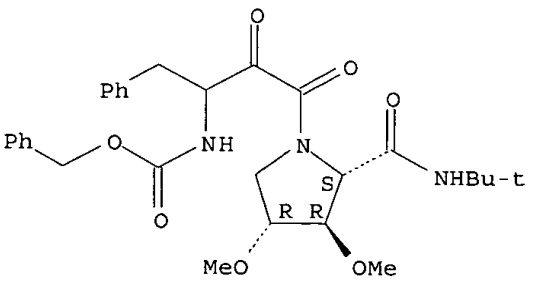
RN 191850-29-0 CAPLUS
CN Carbamic acid, [3-[(2S,4R)-2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191850-30-3 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-dimethoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

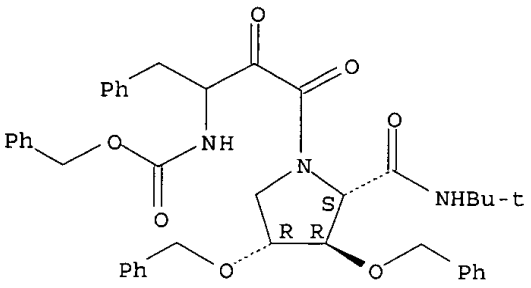
Absolute stereochemistry.



RN 191850-31-4 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-bis(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.)]-[partial]- (9CI) (CA

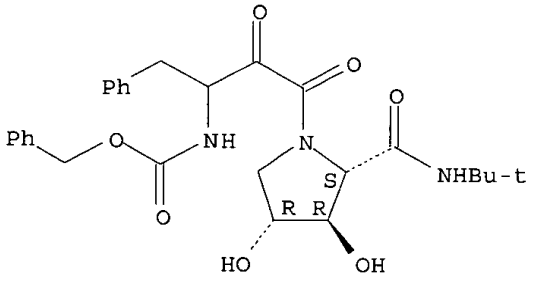
INDEX NAME)

Absolute stereochemistry.



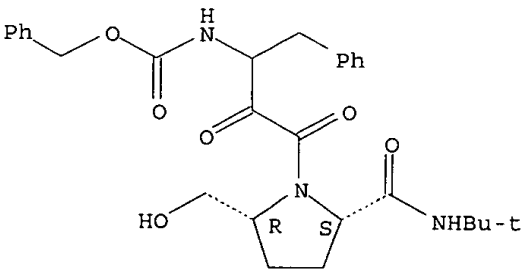
RN 191850-32-5 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-dihydroxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191850-33-6 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-5-(hydroxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

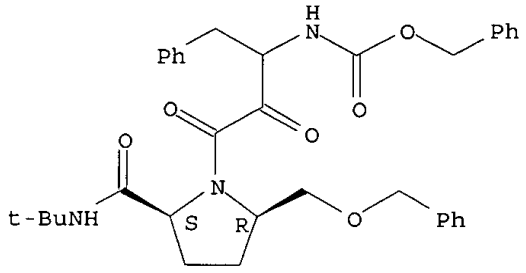
Absolute stereochemistry.



RN 191850-34-7 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-5-

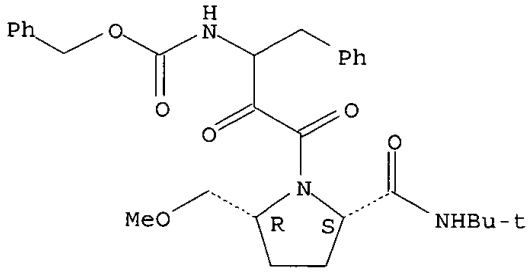
[(phenylmethoxy)methyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



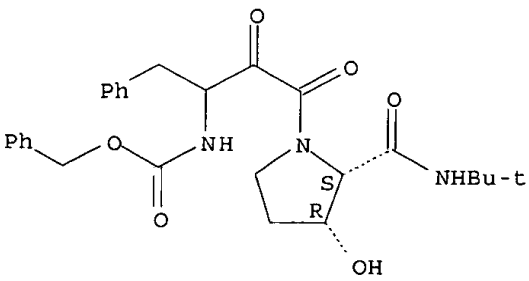
RN 191850-35-8 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



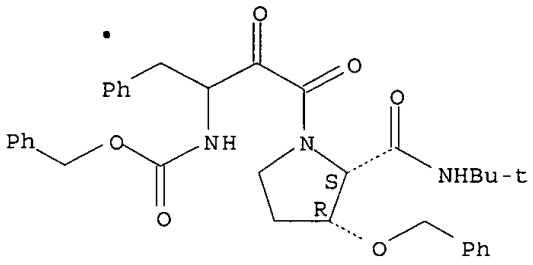
RN 191850-36-9 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3-hydroxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



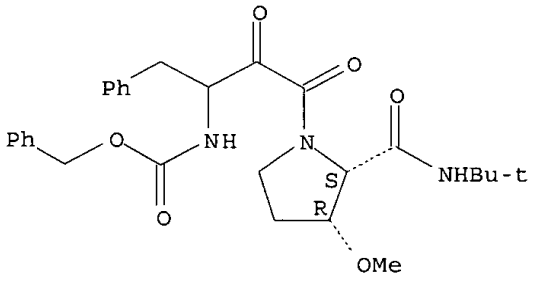
RN 191850-37-0 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



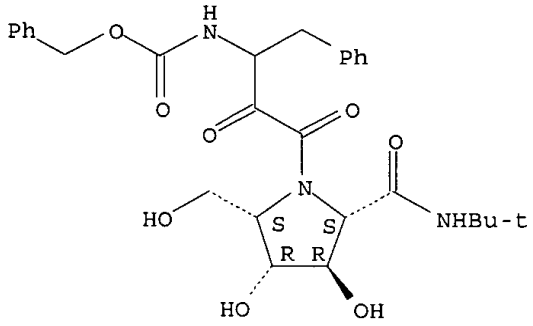
RN 191850-38-1 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



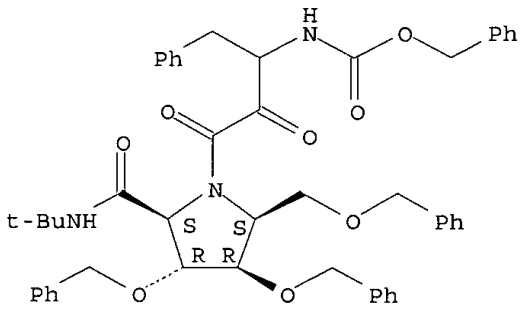
RN 191850-59-6 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-dihydroxy-5-(hydroxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



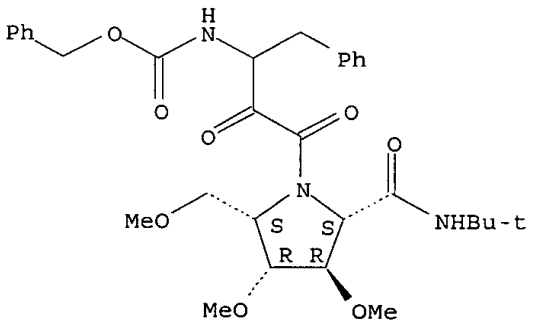
RN 191850-60-9 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-bis(phenylmethoxy)-5-[(phenylmethoxy)methyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191850-61-0 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-dimethoxy-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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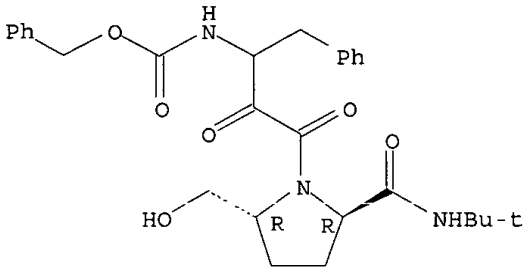
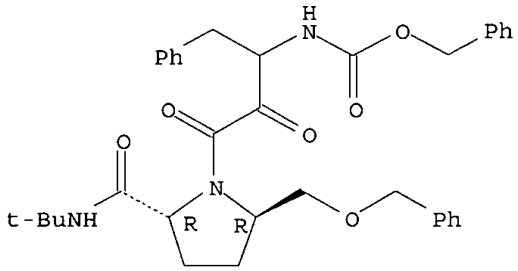
RN 191850-91-6 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-5-(hydroxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2R-(2.alpha.,5.beta.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



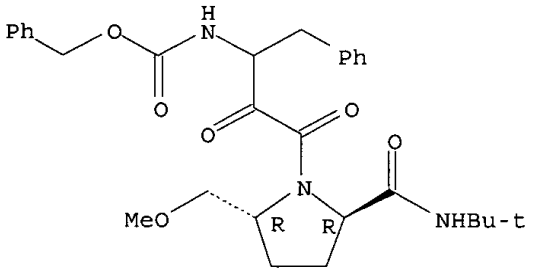
RN 191850-92-7 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-5-[(phenylmethoxy)methyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2R-(2.alpha.,5.beta.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



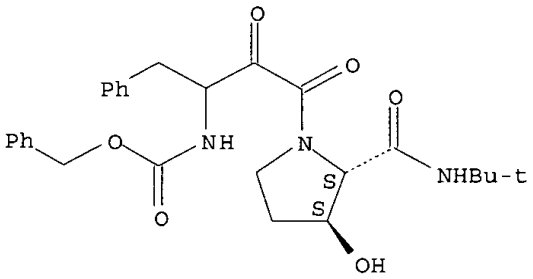
RN 191850-93-8 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2R-(2.alpha.,5.beta.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



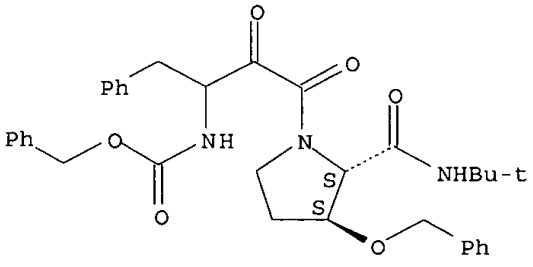
RN 191850-94-9 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3-hydroxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



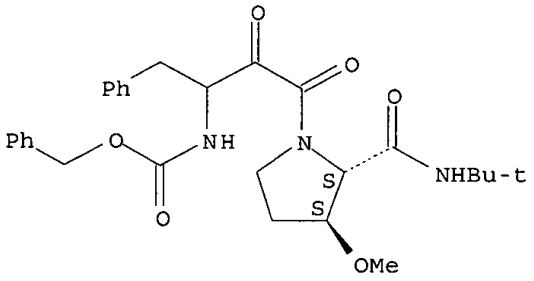
RN 191850-95-0 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



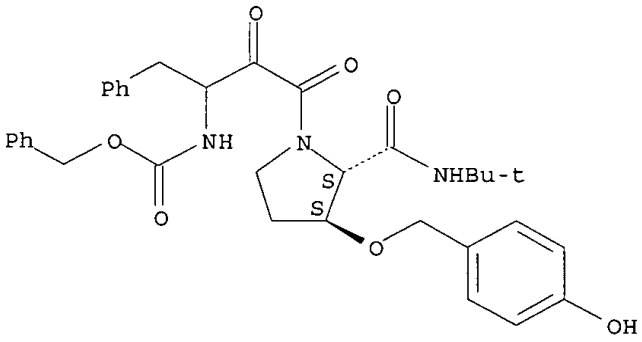
RN 191850-96-1 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



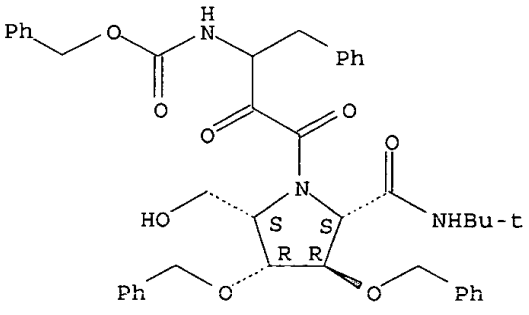
RN 191851-37-3 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3-[(4-hydroxyphenyl)methoxy]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191851-40-8 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-5-(hydroxymethyl)-3,4-bis(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191851-42-0 CAPLUS

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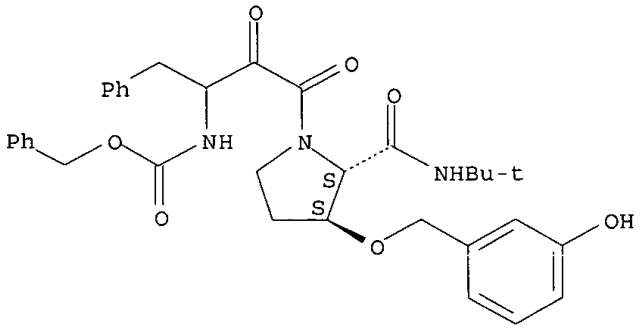
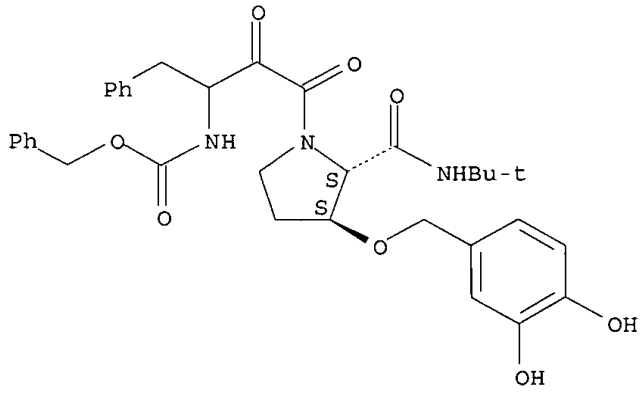
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3-[(3-hydroxyphenyl)methoxy]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191851-43-1 CAPLUS
CN Carbamic acid, [3-[3-[(3,4-dihydroxyphenyl)methoxy]-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.)]-[partial]- (9CI) (CA INDEX NAME)

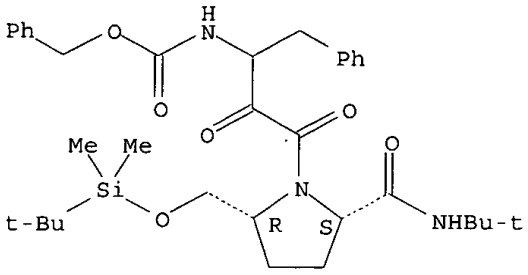
Absolute stereochemistry.



IT **191851-51-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of hydroxyethylamine core structures as HIV and FIV protease inhibitors)
RN 191851-51-1 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-5-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Golam Shameem



L4 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:938815 CAPLUS
DOCUMENT NUMBER: 124:105570
TITLE: Selectivity in the Inhibition of HIV and FIV Protease: Inhibitory and Mechanistic Studies of Pyrrolidine-Containing .alpha.-Keto Amide and Hydroxyethylamine Core Structures
AUTHOR(S): Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.; Gustchina, Alla; Kervinen, Jukka; Zdanov, Alexander; Wlodawer, Alexander; Wong, Chi-Huey
CORPORATE SOURCE: Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1995), 117(48), 11867-78
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

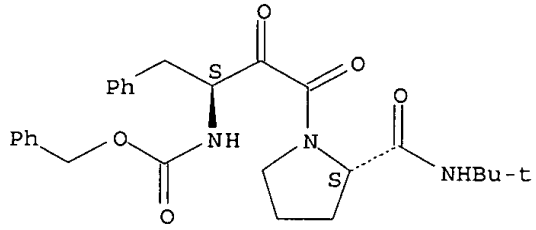
AB This study describes the development of new pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamine core structures as mechanism based inhibitors of the HIV and FIV proteases. The .alpha.-keto amide core structure is approx. 300-fold better than the corresponding hydroxyethylamine isosteric structure and 1300-fold better than the corresponding phosphinic acid deriv. as an inhibitor of the HIV protease. The .alpha.-keto amide is however not hydrated until it is bound to the HIV protease as indicated by the NMR study and the x-ray structural anal. Further anal. of the inhibition activities of hydroxyethylamine isosteres contg. modified pyrrolidine derivs. revealed that a cis-methoxy group at C-4 of the pyrrolidine would improve the binding 5- and 25-fold for the trans-isomer. Of the core structures prepd. as inhibitors of the HIV protease, none show significant inhibitory activity against the mechanistically identical FIV protease, and addnl. complementary groups are needed to improve inhibition.

IT **141197-75-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HIV and FIV proteases inhibition by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)

RN 141197-75-3 CAPLUS
CN Carbamic acid, [(1S)-3-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

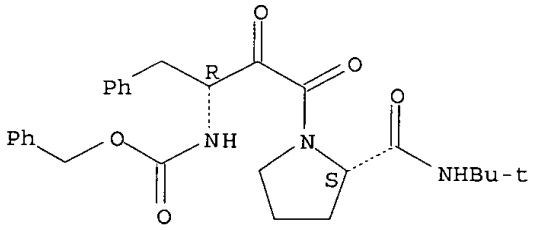
Absolute stereochemistry.

Golam Shameem



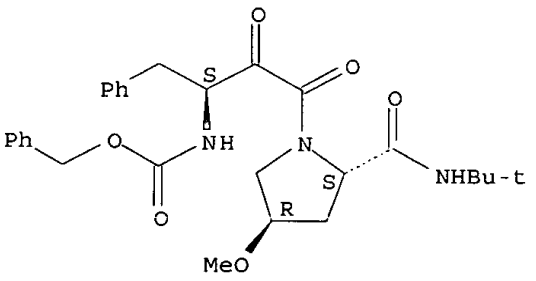
IT **172883-15-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HIV and FIV proteases inhibition by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)
RN 172883-15-7 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **172696-33-2P 172696-34-3P 172823-22-2P**
172823-23-3P 172823-24-4P 172823-25-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction with benzyloxycarbonyl chloride)
RN 172696-33-2 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(R*),2.alpha.,4.beta.]]- (9CI) (CA INDEX NAME)

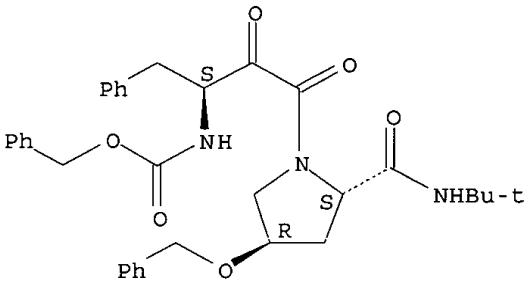
Absolute stereochemistry.



Golam Shameem

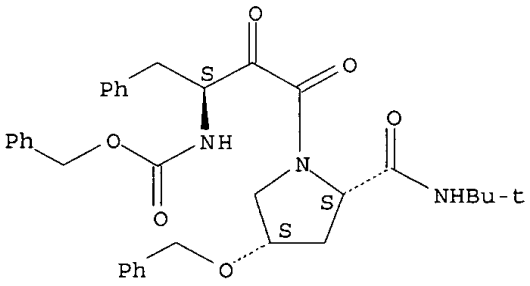
RN 172696-34-3 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(R*),2.alpha.,4.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



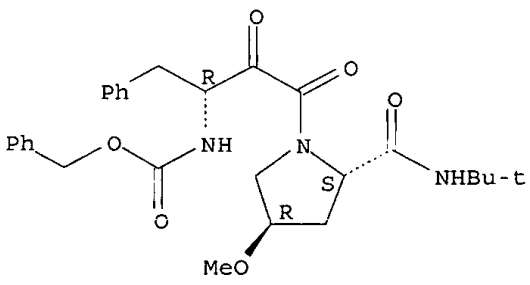
RN 172823-22-2 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(R*),2.alpha.,4.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172823-23-3 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(S*),2.alpha.,4.beta.]]- (9CI) (CA INDEX NAME)

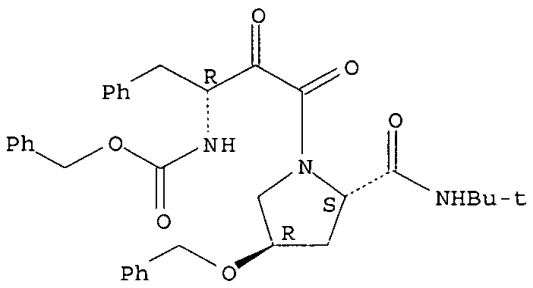
Absolute stereochemistry.



Golam Shameem

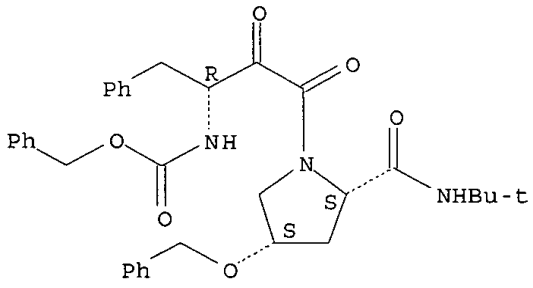
RN 172823-24-4 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(S*),2.alpha.,4.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

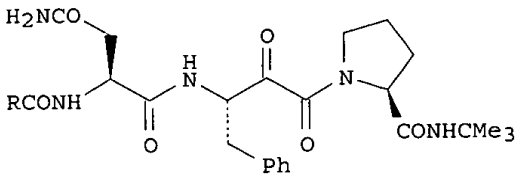


RN 172823-25-5 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(phenylmethoxy)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(S*),2.alpha.,4.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:440143 CAPLUS
DOCUMENT NUMBER: 123:112687
TITLE: Synthesis and human immunodeficiency virus (HIV)-1 protease inhibitory activity of tripeptide analogs containing a dioxoethylene moiety
AUTHOR(S): Kitazaki, Tomoyuki; Asano, Tsuneo; Kato, Koichi; Kishimoto, Shoji; Itoh, Katsumi
CORPORATE SOURCE: Pharmaceutical Research Laboratories III, Takeda Chemical Industries, Ltd., Osaka, 532, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1994), 42(12), 2636-40
CODEN: CPBTAL; ISSN: 0009-2363
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

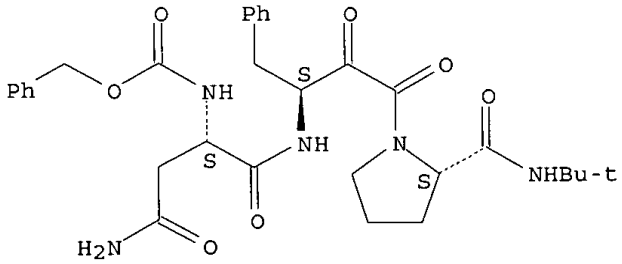
AB Tripeptide analogs I (R = PhCH2O, 2-quinolyl), contg. a dioxoethylene moiety, were designed based on the characteristic structure of the naturally occurring human immunodeficiency virus (HIV)-1 protease inhibitors RPI-856 A, B, C and D. I showed high inhibitory activity, comparable to that of RPI-856 A, against HIV-1 protease in vitro.

IT **141171-73-5P 152843-00-0P 165522-25-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and human immunodeficiency virus-1 protease inhibitory activity of tripeptide analogs contg. a dioxoethylene moiety)

RN 141171-73-5 CAPLUS

CN Carbamic acid, [3-amino-1-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-, phenylmethyl ester, [2S-[1[R*(R*)],2R*]]- (9CI) (CA INDEX NAME)

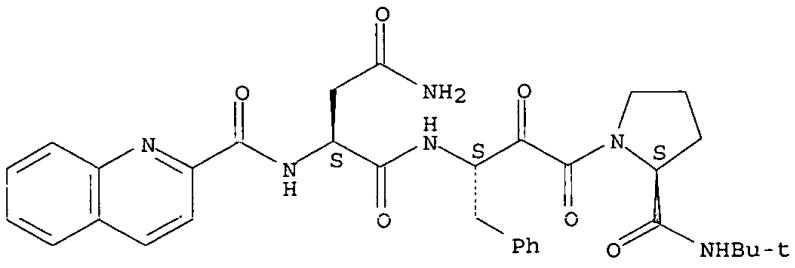
Absolute stereochemistry.



RN 152843-00-0 CAPLUS

CN L-Prolinamide, N2-(2-quinolinylcarbonyl)-L-asparaginyl-2-oxo-4-phenyl-(S)-3-aminobutanoyl-N-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)

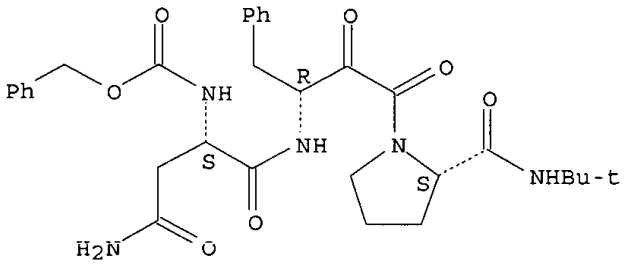
Absolute stereochemistry. Rotation (-).



Golam Shameem

RN 165522-25-8 CAPLUS
CN Carbamic acid, [3-amino-1-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-, phenylmethyl ester, [2S-[1[S*(R*)],2R*]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



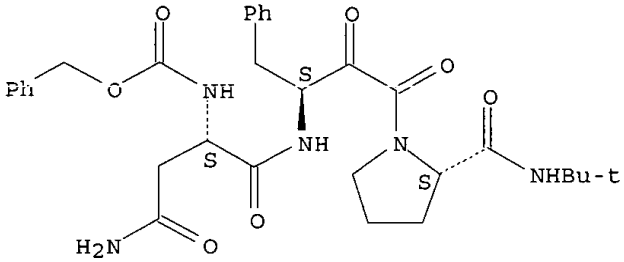
L4 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:289408 CAPLUS
DOCUMENT NUMBER: 120:289408
TITLE: Three-dimensional QSAR of human immunodeficiency virus (I) protease inhibitors. 1. A CoMFA study employing experimentally-determined alignment rules
AUTHOR(S): Waller, Chris L.; Oprea, Tudor I.; Giolitti, Alessandro; Marshall, Garland R.
CORPORATE SOURCE: Cent. Mol. Des., Washington Univ., St. Louis, MO, 63130, USA
SOURCE: Journal of Medicinal Chemistry (1993), 36(26), 4152-60
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Comparative mol. field anal. (CoMFA), a 3-dimensional, quant. structure-activity relationship (QSAR) paradigm, was used to exam. the correlations between the calcd. physicochem. properties and in the vitro activities of a series of human immunodeficiency virus (HIV-1) protease inhibitors. The training set consisted of 59 mols. from five structurally-diverse transition-state isostere classes: hydroxyethylamine, statine, norstatine, keto amide, and dihydroxyethylene. The availability of x-ray crystallog. data for at least one representative from each class bound to the protease provided information regarding not only the active conformation of each ligand but also, via superimposition of protease backbones, the relative positions of each ligand with respect to one another in the active site of the enzyme. Once aligned, these mols. served as templates on which addnl. congeners were field-fit minimized. Addnl. alignment rules were derived from minimization of the ligands in the active site of the semirigid protease. The predictive ability of each resultant model was evaluated using a test set comprised of mols. contg. a novel transition-state isostere: hydroxyethylurea. Crystallog. studies indicated an unexpected binding mode for this series of compds. which precluded the use of the field-fit minimization alignment technique. The test set mols. were, therefore, subjected to a limited systematic search in conjunction with active-site minimization. The conformer of each mol. expressing the lowest interaction energy with the active site was included in the test set. Field-fit minimization of neutral mols. to crystal ligands and active-site minimizations of protonated ligands yielded predictive correlations for HIV-1 protease inhibitors. The use of

crystallog. data in the detn. of alignment rules and field-fit minimization as a mol. alignment tool in the absence of direct exptl. data regarding binding modes is strongly supported by these results.

IT **141171-73-5 141197-75-3**
RL: BIOL (Biological study)
(human immunodeficiency virus 1 protease inhibition by, QSAR of)

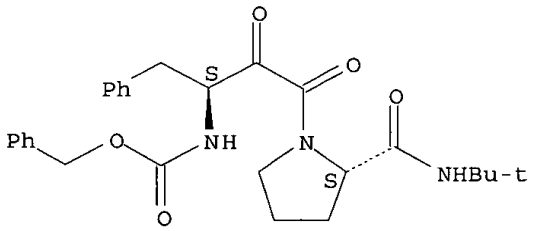
RN 141171-73-5 CAPLUS
CN Carbamic acid, [3-amino-1-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-, phenylmethyl ester, [2S-[1[R*(R*)],2R*]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 141197-75-3 CAPLUS
CN Carbamic acid, [(1S)-3-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:245780 CAPLUS
DOCUMENT NUMBER: 120:245780
TITLE: Preparation of asparagine-containing peptide derivatives as retrovirus protease inhibitors
INVENTOR(S): Ito, Katsumi; Kato, Koichi
PATENT ASSIGNEE(S): Takeda Chemical Industries Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 14 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

JP 05178824	A2	19930720	JP 1992-159678	19920618
PRIORITY APPLN. INFO.:			JP 1991-195469	19910805

OTHER SOURCE(S): MARPAT 120:245780

GI For diagram(s), see printed CA Issue.

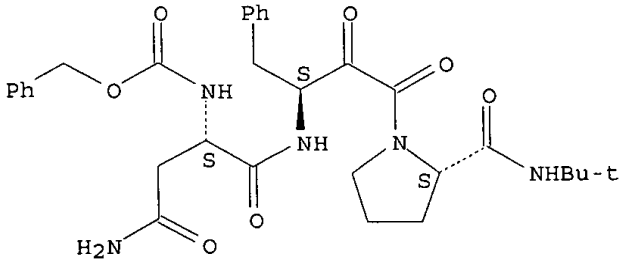
AB The title compds. (I; ring A = 5- to 6-membered ring; R1 = R2 = H or R1R2 forms a fused ring; R3 = optionally esterified or amidated CO2H; R4 = H, acyl; X = CHOH, CO), useful for the treatment of diseases caused by retroviruses, e.g. human immunodeficiency virus (HIV) causing AIDS, adult T-cell leukemia virus (ATLV), human T-cell leukemia virus type I (HTLV-I), and T-cell hairycell leukemia, are prepd. Thus, H-Pro-NHCMe3 was condensed with (2RS,3S)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutanoic acid in the presence of (EtO)2P(O)CN and Et3N in DMF to give N.alpha.-[(3S)-3-benzyloxycarbonylamino-2-hydroxy-4-phenylbutyryl]-N-tert-butyl-L-prolinamide as a diastereomeric mixt., which (more polar diastereomer) was hydrogenolyzed over 10% Pd-C in aq. MeOH to give N.alpha.-[(3S)-3-amino-2-hydroxy-4-phenylbutyryl]-N-tert-butyl-L-prolinamide. The latter was condensed with Boc-Asn-C6H4NO2-p in DMF to give N.alpha.-[(3S)-3-(N.alpha.-benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutyryl]-N-tert-butyl-L-prolinamide, which showed IC50 of 0.020 .mu.M against recombinant HIV-1 protease. Addnl. 3 were prepd.

IT **141171-73-5P 152843-00-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as retrovirus protease inhibitor)

RN 141171-73-5 CAPLUS

CN Carbamic acid, [3-amino-1-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-, phenylmethyl ester, [2S-[1[R*(R*)],2R*]]- (9CI) (CA INDEX NAME)

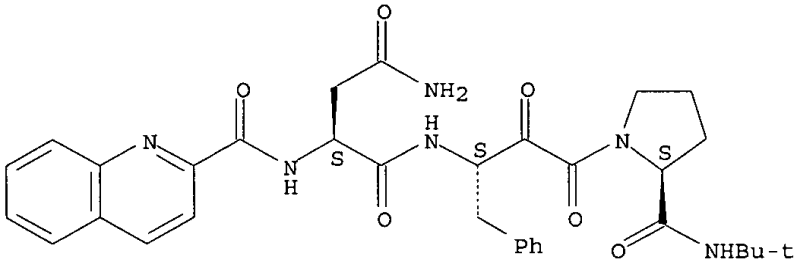
Absolute stereochemistry.



RN 152843-00-0 CAPLUS

CN L-Prolinamide, N2-(2-quinolinylcarbonyl)-L-asparaginyl-2-oxo-4-phenyl-(S)-3-aminobutanoyl-N-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)

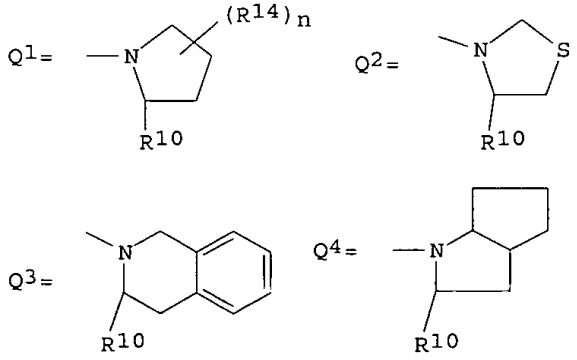
Absolute stereochemistry. Rotation (-).



L4 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:245776 CAPLUS
DOCUMENT NUMBER: 120:245776
TITLE: Preparation of cyclic amides of 3-amino-2-hydroxycarboxylic acids as HIV protease inhibitors
INVENTOR(S): Krantz, Alexander; Tam, Tim Fat; Castelhano, Arlindo Lucas; Nestor, John Joseph, Jr.
PATENT ASSIGNEE(S): Syntex (U.S.A.), Inc., USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9313066	A1	19930708	WO 1992-US10772	19921218
W: AU, CA, FI, HU, JP, KR, NO, NZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9332782	A1	19930728	AU 1993-32782	19921218
ZA 9209869	A	19940620	ZA 1992-9869	19921218
PRIORITY APPLN. INFO.:			US 1991-812905	19911220
			WO 1992-US10772	19921218

OTHER SOURCE(S): MARPAT 120:245776
GI



AB R1R2NCHR3CONHCHR4CR5R6COR7 [R1 = (ar)alkoxycarbonyl, (substituted)

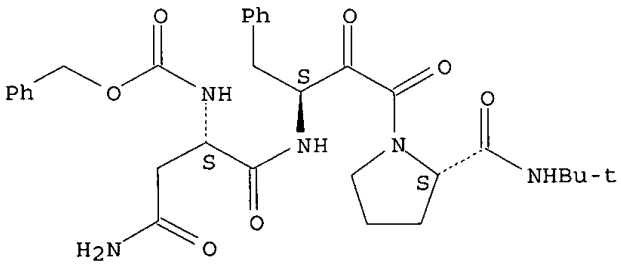
Golam Shameem

aralkanoyl, aroyl, heterocyclylcarbonyl, aryloxyalkanoyl, carbamoyl, heterocyclyloxyalkanoyl; R2, R5 = H; R3 = (substituted) alkyl, R4 = (substituted) aryl, aralkyl; R6 = OH; R5R6 = O; R1 = Q1-Q4, etc.; n = 0-2; R10 = alkoxycarbonyl, (substituted) carbamoyl; R14 = OH, alkyl, alkoxy, Ph], were prepd. Thus, N'-tert-Bu prolinamide (prepn. given) was coupled with (2S,3S)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoic acid using EDCI/hydroxybenzotriazole in DMF to give 1-[(2S,3S)-3-(benzyloxycarbonyl-L-asparaginyl)amino-2-hydroxy-4-phenylbutanoyl]-N'-tert-butyl-L-prolinamide. I inhibited HIV protease with IC50 = 0.49-30 nM. I dosage formulations are given.

IT **141171-73-5P 141197-75-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as HIV protease inhibitor)

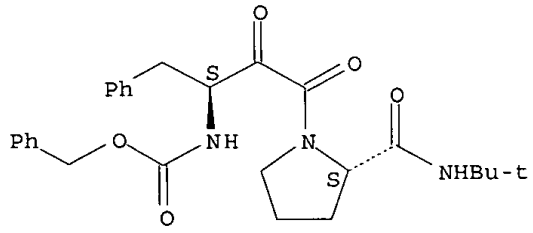
RN 141171-73-5 CAPLUS
CN Carbamic acid, [3-amino-1-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo 1 (phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-, phenylmethyl ester, [2S-[1[R*(R*)],2R*]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 141197-75-3 CAPLUS
CN Carbamic acid, [(1S)-3-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:227702 CAPLUS
DOCUMENT NUMBER: 116:227702
TITLE: Intriguing structure-activity relations underlie the potent inhibition of HIV protease by norstatine-based peptides

Golam Shameem

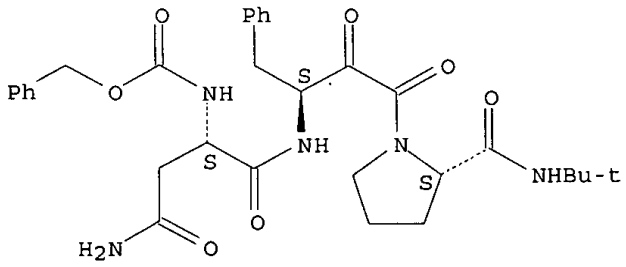
AUTHOR(S): Tam, Tim F.; Carriere, Julie; MacDonald, I. David; Castelhano, Arlindo L.; Pliura, Diana H.; Dewdney, Nolan J.; Thomas, Everton M.; Bach, Chinh; Barnett, Jimmy; et al.
CORPORATE SOURCE: Syntex Res. Canada, Mississauga, ON, L5N 3X4, Can.
SOURCE: Journal of Medicinal Chemistry (1992), 35(7), 1318-20
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Phenylnorstatine contg. peptides extending from the P2 to P1' positions, with L-proline at the P1' position and S-stereochem. of the P1 component, exhibit impressive potency vs. HIV-1 potease (IC50 = 0.58-7.4 nM). Representative ketoamides are also active with slightly lower potency. Analogous hydroxyethylamines have previously been reported to be potent inhibitors of this enzyme. The presence of an addnl. carbonyl in this series of proline-based inhibitors enhances their potency, and alters structure-activity relations profoundly. Whereas divergent effects on potency have been obsd. for epimeric hydroxyethylamines upon extension of such P1' terminal peptides to P3' with Ile-Val, lengthening of norstatine contg.-inhibitors in the same fashion, dramatically increases the potency of the R-diastereomer and leaves the IC50 of the S-epimer essentially unchanged. Most interestingly, amino acid residues in the P1' position contg. parent and fused piperidines lower activity in the norstatine series. By contrast, significant enhancements in inhibitor potency were reported in the hydroxyethylamine series for such proline replacements. Conformational preferences of 6 member rings influenced by A1,3-strain may contribute to the redn. in potency obsd. for the norstatine contg. peptides.

IT **141171-73-5 141197-75-3**
RL: BIOL (Biological study)
(human immunodeficiency virus 1 protease inhibition by)

RN 141171-73-5 CAPLUS
CN Carbamic acid, [3-amino-1-[[[3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]amino]carbonyl]-3-oxopropyl]-, phenylmethyl ester, [2S-[1[R*(R*)],2R*]]- (9CI) (CA INDEX NAME)

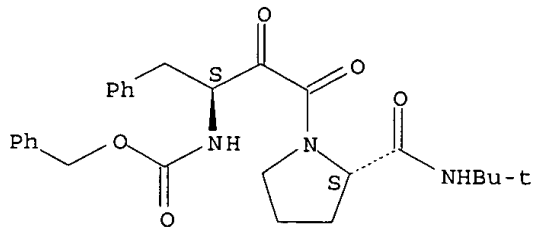
Absolute stereochemistry.



RN 141197-75-3 CAPLUS
CN Carbamic acid, [(1S)-3-[(2S)-2-[[(1,1-dimethylethyl)amino]carbonyl]-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Golam Shameem

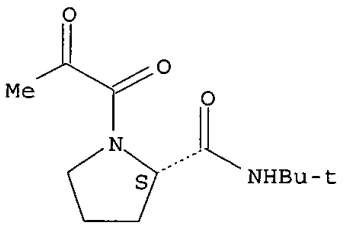


L4 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:591883 CAPLUS
DOCUMENT NUMBER: 113:191883
TITLE: Diastereoselective catalytic hydrogenation of N.alpha.-pyruvoyl-(S)-prolinamide
AUTHOR(S): Munegumi, Toratane; Maruyama, Tetsuya; Takasaki, Michiaki; Harada, Kaoru
CORPORATE SOURCE: Dep. Chem., Univ. Tsukuba, Tsukuba, 305, Japan
SOURCE: Bulletin of the Chemical Society of Japan (1990), 63(6), 1832-4
CODEN: BCSJA8; ISSN: 0009-2673
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 113:191883

AB Catalytic hydrogenation of MeCOCO-Pro-NHR (R = CHMe2, CMe3) over Pd/C in several solvents resulted in the formation of (S)-HOCHMeCO-Pro-NHR in diastereomeric excesses up tp 77%. Usefulness of proline isopropylamide as an asym. moiety is described in the catalytic hydrogenation.

IT **130226-73-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and asym. hydrogenation of, over palladium)
RN 130226-73-2 CAPLUS
CN 2-Pyrrolidinecarboxamide, N-(1,1-dimethylethyl)-1-(1,2-dioxopropyl)-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL

Golam Shameem

	ENTRY	SESSION
CA SUBSCRIBER PRICE	-7.81	-7.81

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STRUCTURE FILE UPDATES: 2 JAN 2003 HIGHEST RN 478001-04-6
DICTIONARY FILE UPDATES: 2 JAN 2003 HIGHEST RN 478001-04-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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Uploading 09077712a.str

L6 STRUCTURE UPLOADED

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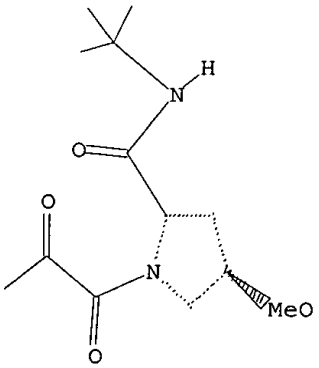
L6 HAS NO ANSWERS
L6 STR



Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SEARCH INITIATED 14:24:34 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 5 TO ITERATE

100.0% PROCESSED 5 ITERATIONS 0 ANSWERS

Golam Shameem

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 5 TO 234
PROJECTED ANSWERS: 0 TO 0

L7 0 SEA SSS SAM L6

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FULL SEARCH INITIATED 14:24:42 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 172 TO ITERATE

100.0% PROCESSED 172 ITERATIONS 6 ANSWERS
SEARCH TIME: 00.00.01

L8 6 SEA SSS FUL L6

=> FIL CAPLUS
COST IN U.S. DOLLARS

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FULL ESTIMATED COST	148.15	356.83

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-7.81

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FILE COVERS 1907 - 3 Jan 2003 VOL 138 ISS 2
FILE LAST UPDATED: 2 Jan 2003 (20030102/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> s l8
L9 3 L8

=> d ibib abs hitstr l9 tot

L9 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS

Golam Shameem

ACCESSION NUMBER: 2001:801933 CAPLUS
DOCUMENT NUMBER: 137:226
TITLE: A study on docking mode of HIV protease and their inhibitors
AUTHOR(S): Akaho, Eiichi; Morris, Garret; Goodsell, David; Wong, David; Olson, Arthur
CORPORATE SOURCE: Fac. Pharmacetuical Sci., Kobe Gakuin Univ., 518 Arise, Ikawadani-cho, Nishi-ku, Kobe, 651-2180, Japan
SOURCE: Journal of Chemical Software (2001), 7(3), 103-114
CODEN: CHSFEC; ISSN: 0918-0761
PUBLISHER: Kagaku Sofutowea Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: English

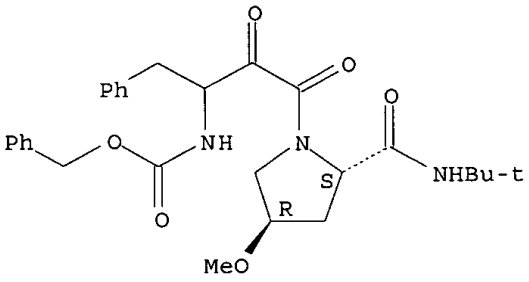
AB The capability to propose feasible ways of binding a putative ligand inhibitor to a known receptor site is crucial to the successful structure-based drug design. A computer docking approach is to position or "dock" ligand and receptor mols. together in many different ways and then score each orientation by applying a reasonable evaluation function. AutoDock3.0 is an unbiased type docking program in which a user does not have to direct a ligand to an active site, but the system finds an optimal position after a ligand is placed in a random manner. Synthesized derivs. of the intact inhibitor (inh1) of HIV protease were investigated for their docking modes as compared with their Ki values. Among the derivs., inh3trans and inh6H were found to be more powerful inhibitors of HIV protease than the others. Gibbs free energy calcd. by applying mol. mechanics interaction energies was compared with the one obtained by using exptl. inhibitory potencies for a series of HIV protease inhibitors, and a fairly good correlation was found between the two. Based on this favorable correlationship between the computational and the exptl. results, the computational expts. were pursued for the compds. drawn by Sybyl taking into consideration the fact that unexploited carbon affinity regions (or hydrophobic regions) with sizable vol. were detected on the docking study of inh1 and inh8 against HIV protease. Those were compds. with a t-Bu substituted by various hydrophobic side chains. Among those a compd. with a benzyl group exhibited the lowest docking energy. Since one of the goals of this paper was to perform the computational drug-design expt. to investigate potential HIV protease inhibitors, the authors would like to leave the clin. investigational work for the expertise of those areas.

IT **191850-28-9**
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(docking mode of HIV protease and their inhibitors)

RN 191850-28-9 CAPLUS
CN Carbamic acid, [3-[(2S,4R)-2-[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Golam Shameem



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:473732 CAPLUS
DOCUMENT NUMBER: 127:81793
TITLE: Preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors
INVENTOR(S): Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
PATENT ASSIGNEE(S): Scripps Research Institute, USA; Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
SOURCE: PCT Int. Appl., 202 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9721100	A1	19970612	WO 1996-US19571	19961209
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2238337	AA	19970612	CA 1996-2238337	19961209
AU 9712844	A1	19970627	AU 1997-12844	19961209
AU 728373	B2	20010111		
EP 873519	A1	19981028	EP 1996-943657	19961209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2000502332	T2	20000229	JP 1997-521485	19961209

PRIORITY APPLN. INFO.: US 1995-568532 A2 19951207
WO 1996-US19571 W 19961209

OTHER SOURCE(S): MARPAT 127:81793
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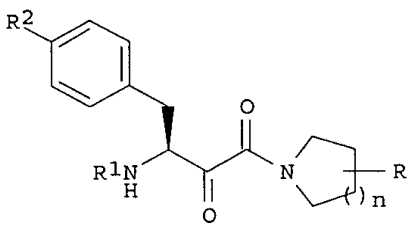

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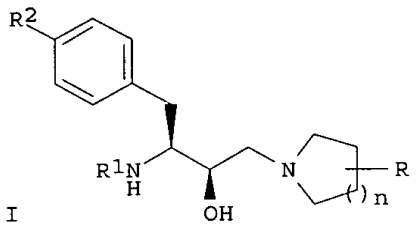

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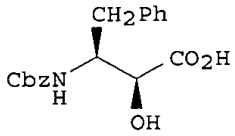

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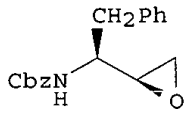


IV

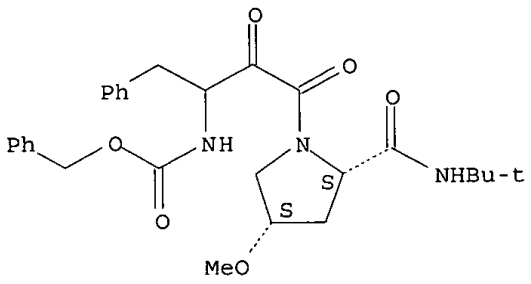
AB Combinatorial libraries of HIV and FIV protease inhibitors are characterized by .alpha.-keto amide or hydroxyethylamine core structures I and II [n = 1, 2; R = one or more groups CONHCMe3, CH2OH, CH2OMe, CH2OCH2Ph, OH, OCH2Ph, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy, etc.; R1 = PhCH2O2C (Cbz), Me3CO2C (Boc), acyl; R2 = H, HO, PhCH2O, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy] flanked by on one side by substituted pyrrolidines, piperidines, or azasugars and on the other side by Phe, Tyr, or substituted tyrosines. The libraries are synthesized via coupling of the nitrogen heterocycles with hydroxy acids, e.g. III, followed by oxidn. to the keto amide, or a one-step coupling with epoxides, e.g. IV. Highly efficacious drug candidates are identified by screening the libraries for binding and inhibitory activity against both HIV and FIV protease. Drug candidates displaying clin. useful activity against both HIV and FIV protease are identified as being potentially resistive against a loss of inhibitory activity due to development of resistant strains of HIV.

IT **191850-27-8P 191850-28-9P 191850-30-3P**
191850-61-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

RN 191850-27-8 CAPLUS

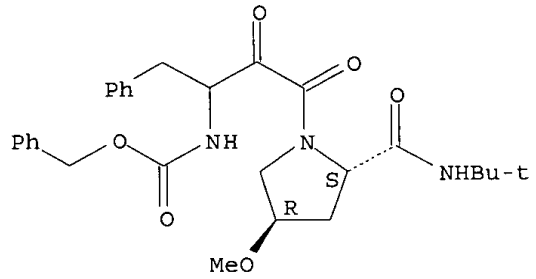
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,4.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



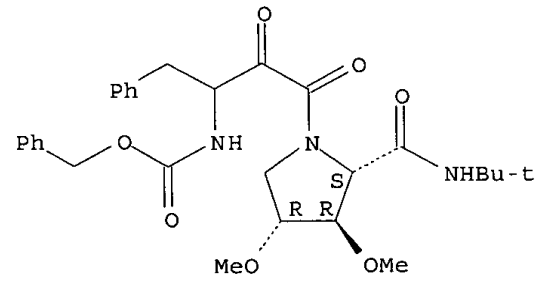
RN 191850-28-9 CAPLUS
CN Carbamic acid, [3-[(2S,4R)-2-[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



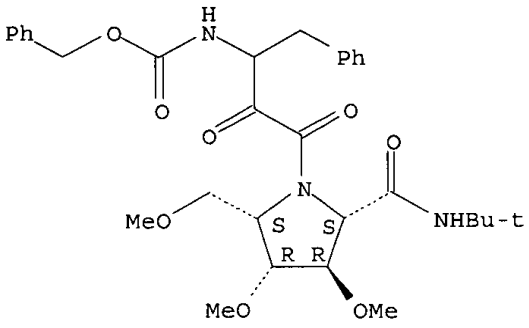
RN 191850-30-3 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-dimethoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191850-61-0 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-dimethoxy-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



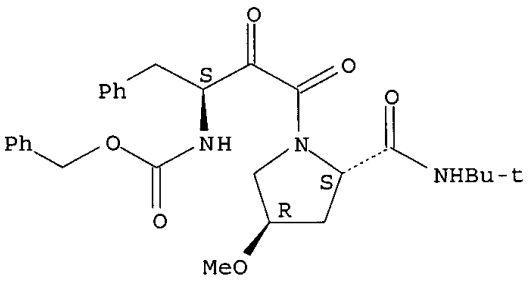
L9 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:938815 CAPLUS
DOCUMENT NUMBER: 124:105570
TITLE: Selectivity in the Inhibition of HIV and FIV Protease: Inhibitory and Mechanistic Studies of Pyrrolidine-Containing .alpha.-Keto Amide and Hydroxyethylamine Core Structures
AUTHOR(S): Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.; Gustchina, Alla; Kervinen, Jukka; Zdanov, Alexander; Wlodawer, Alexander; Wong, Chi-Huey
CORPORATE SOURCE: Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1995), 117(48), 11867-78.
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study describes the development of new pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamine core structures as mechanism based inhibitors of the HIV and FIV proteases. The .alpha.-keto amide core structure is approx. 300-fold better than the corresponding hydroxyethylamine isosteric structure and 1300-fold better than the corresponding phosphinic acid deriv. as an inhibitor of the HIV protease. The .alpha.-keto amide is however not hydrated until it is bound to the HIV protease as indicated by the NMR study and the x-ray structural anal. Further anal. of the inhibition activities of hydroxyethylamine isosteres contg. modified pyrrolidine derivs. revealed that a cis-methoxy group at C-4 of the pyrrolidine would improve the binding 5- and 25-fold for the trans-isomer. Of the core structures prepd. as inhibitors of the HIV protease, none show significant inhibitory activity against the mechanistically identical FIV protease, and addnl. complementary groups are needed to improve inhibition.

IT **172696-33-2P 172823-23-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction with benzyloxycarbonyl chloride)

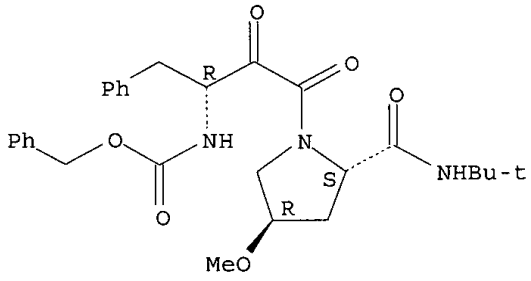
RN 172696-33-2 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(R*),2.alpha.,4.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172823-23-3 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-methoxy-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(S*),2.alpha.,4.beta.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	16.53	373.36

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.95	-9.76

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STRUCTURE FILE UPDATES: 2 JAN 2003 HIGHEST RN 478001-04-6
DICTIONARY FILE UPDATES: 2 JAN 2003 HIGHEST RN 478001-04-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when

conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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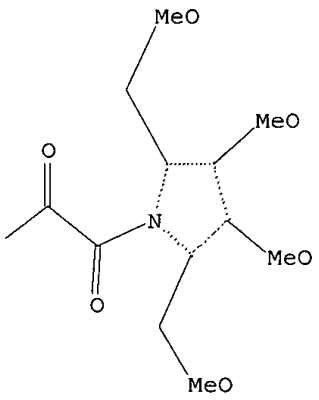
Uploading 09077712b.str

L10 STRUCTURE UPLOADED

=> d l10
L10 HAS NO ANSWERS
L10 STR



Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED - 0 TO ITERATE

100.0% PROCESSED 0 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 0 TO 0
PROJECTED ANSWERS: 0 TO 0

L11 0 SEA SSS SAM L10

=> s l1o sss full
L12 0 L1O

=> s l10 sss full
FULL SEARCH INITIATED 14:30:48 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 10 TO ITERATE

Golam Shameem

100.0% PROCESSED 10 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

L13 2 SEA SSS FUL L10

=> FIL CAPLUS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	153.57	526.93

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-9.76

FILE 'CAPLUS' ENTERED AT 14:31:00 ON 03 JAN 2003
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FILE COVERS 1907 - 3 Jan 2003 VOL 138 ISS 2
FILE LAST UPDATED: 2 Jan 2003 (20030102/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> s l13
L14 2 L13

=> d ibib abs hitstr l14 tot

L14 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:473732 CAPLUS
DOCUMENT NUMBER: 127:81793
TITLE: Preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors
INVENTOR(S): Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
PATENT ASSIGNEE(S): Scripps Research Institute, USA; Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
SOURCE: PCT Int. Appl., 202 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

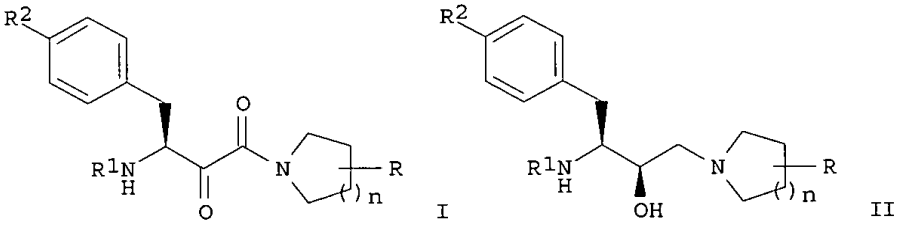
Golam Shameem

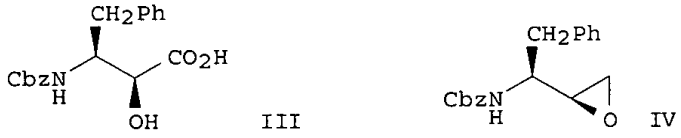
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9721100	A1	19970612	WO 1996-US19571	19961209
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2238337	AA	19970612	CA 1996-2238337	19961209
AU 9712844	A1	19970627	AU 1997-12844	19961209
AU 728373	B2	20010111		
EP 873519	A1	19981028	EP 1996-943657	19961209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2000502332	T2	20000229	JP 1997-521485	19961209

PRIORITY APPLN. INFO.: US 1995-568532 A2 19951207
WO 1996-US19571 W 19961209

OTHER SOURCE(S): MARPAT 127:81793

GI





AB Combinatorial libraries of HIV and FIV protease inhibitors are characterized by .alpha.-keto amide or hydroxyethylamine core structures I and II [n = 1, 2; R = one or more groups CONHCMe3, CH2OH, CH2OMe, CH2OCH2Ph, OH, OCH2Ph, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy, etc.; R1 = PhCH2O2C (Cbz), Me3CO2C (Boc), acyl; R2 = H, HO, PhCH2O, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy] flanked by on one side by substituted pyrrolidines, piperidines, or azasugars and on the other side by Phe, Tyr, or substituted tyrosines. The libraries are synthesized via coupling of the nitrogen heterocycles with hydroxy acids, e.g. III, followed by oxidn. to the keto amide, or a one-step coupling with epoxides, e.g. IV. Highly efficacious drug candidates are identified by screening the libraries for

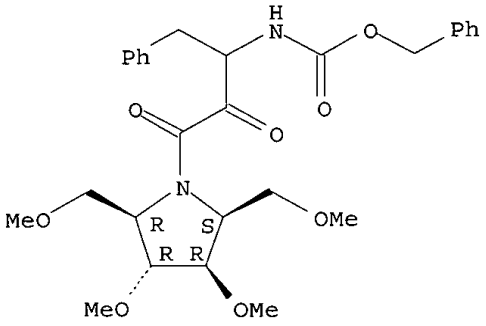
binding and inhibitory activity against both HIV and FIV protease. Drug candidates displaying clin. useful activity against both HIV and FIV protease are identified as being potentially resistive against a loss of inhibitory activity due to development of resistant strains of HIV.

IT **191849-90-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

RN 191849-90-8 CAPLUS

CN Carbamic acid, [3-[3,4-dimethoxy-2,5-bis(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2R-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:938815 CAPLUS

DOCUMENT NUMBER: 124:105570

TITLE: Selectivity in the Inhibition of HIV and FIV Protease: Inhibitory and Mechanistic Studies of Pyrrolidine-Containing .alpha.-Keto Amide and Hydroxyethylamine Core Structures

AUTHOR(S): Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.; Gustchina, Alla; Kervinen, Jukka; Zdanov, Alexander; Wlodawer, Alexander; Wong, Chi-Huey

CORPORATE SOURCE: Scripps Research Institute, La Jolla, CA, 92037, USA

SOURCE: Journal of the American Chemical Society (1995), 117(48), 11867-78
CODEN: JACSAT; ISSN: 0002-7863

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study describes the development of new pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamine core structures as mechanism based inhibitors of the HIV and FIV proteases. The .alpha.-keto amide core structure is approx. 300-fold better than the corresponding hydroxyethylamine isosteric structure and 1300-fold better than the corresponding phosphinic acid deriv. as an inhibitor of the HIV protease. The .alpha.-keto amide is however not hydrated until it is bound to the HIV protease as indicated by the NMR study and the x-ray structural anal. Further anal. of the inhibition activities of hydroxyethylamine isosteres

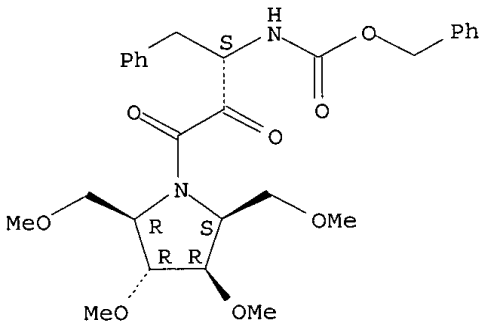
contg. modified pyrrolidine derivs. revealed that a cis-methoxy group at C-4 of the pyrrolidine would improve the binding 5- and 25-fold for the trans-isomer. Of the core structures prepd. as inhibitors of the HIV protease, none show significant inhibitory activity against the mechanistically identical FIV protease, and addnl. complementary groups are needed to improve inhibition.

IT **172696-19-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HIV and FIV proteases inhibition by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)

RN 172696-19-4 CAPLUS

CN Carbamic acid, [3-[3,4-dimethoxy-2,5-bis(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(R*),2.alpha.,3.alpha.,4.beta.,5.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction with benzyloxycarbonyl chloride

=> FIL REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	9.91	536.84

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.30	-11.06

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STRUCTURE FILE UPDATES: 2 JAN 2003 HIGHEST RN 478001-04-6
DICTIONARY FILE UPDATES: 2 JAN 2003 HIGHEST RN 478001-04-6

Golam Shameem

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

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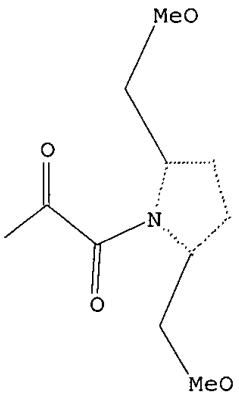
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09077712c.str

L15 STRUCTURE UPLOADED

=> d l15
L15 HAS NO ANSWERS
L15 STR



Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED - 23 TO ITERATE

100.0% PROCESSED 23 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 173 TO 747
PROJECTED ANSWERS: 0 TO 0

L16 0 SEA SSS SAM L15

=> s l15 sss full
FULL SEARCH INITIATED 14:32:44 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 395 TO ITERATE

Golam Shameem

100.0% PROCESSED 395 ITERATIONS 4 ANSWERS
SEARCH TIME: 00.00.01

L17 4 SEA SSS FUL L15

=> FIL CAPLUS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	148.15	684.99

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-11.06

FILE 'CAPLUS' ENTERED AT 14:32:49 ON 03 JAN 2003
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FILE COVERS 1907 - 3 Jan 2003 VOL 138 ISS 2
FILE LAST UPDATED: 2 Jan 2003 (20030102/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> s l17
L18 3 L17

=> d ibib abs hitstr l18 tot

L18 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:473732 CAPLUS
DOCUMENT NUMBER: 127:81793
TITLE: Preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors
INVENTOR(S): Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
PATENT ASSIGNEE(S): Scripps Research Institute, USA; Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
SOURCE: PCT Int. Appl., 202 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

Golam Shameem

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9721100	A1	19970612	WO 1996-US19571	19961209
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2238337	AA	19970612	CA 1996-2238337	19961209
AU 9712844	A1	19970627	AU 1997-12844	19961209
AU 728373	B2	20010111		
EP 873519	A1	19981028	EP 1996-943657	19961209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2000502332	T2	20000229	JP 1997-521485	19961209

PRIORITY APPLN. INFO.: US 1995-568532 A2 19951207
WO 1996-US19571 W 19961209

OTHER SOURCE(S): MARPAT 127:81793

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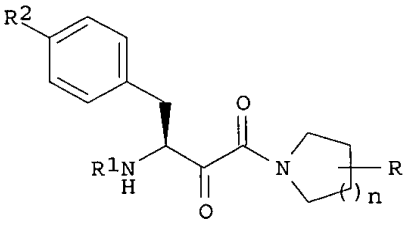

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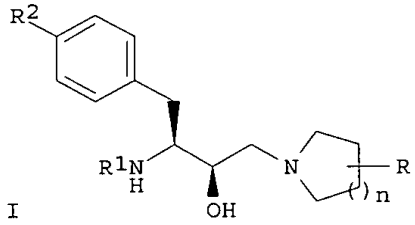

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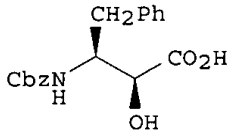

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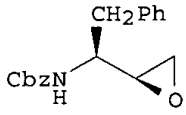


IV

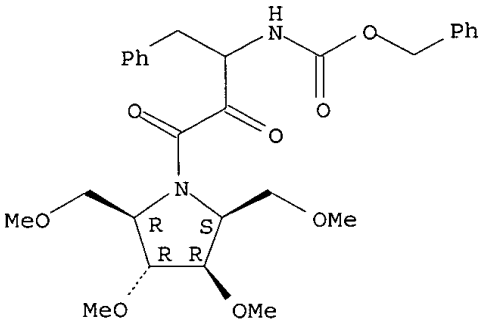
AB Combinatorial libraries of HIV and FIV protease inhibitors are characterized by .alpha.-keto amide or hydroxyethylamine core structures I and II [n = 1, 2; R = one or more groups CONHCMe3, CH2OH, CH2OMe, CH2OCH2Ph, OH, OCH2Ph, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy, etc.; R1 = PhCH2O2C (Cbz), Me3CO2C (Boc), acyl; R2 = H, HO, PhCH2O, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy] flanked by on one side by substituted pyrrolidines, piperidines, or azasugars and on the other side by Phe, Tyr, or substituted tyrosines. The libraries are synthesized via coupling of the nitrogen heterocycles with hydroxy acids, e.g. III, followed by oxidn. to the keto amide, or a one-step coupling with epoxides, e.g. IV. Highly efficacious drug candidates are identified by screening the libraries for

binding and inhibitory activity against both HIV and FIV protease. Drug candidates displaying clin. useful activity against both HIV and FIV protease are identified as being potentially resistive against a loss of inhibitory activity due to development of resistant strains of HIV.

IT **191849-90-8P 191850-25-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

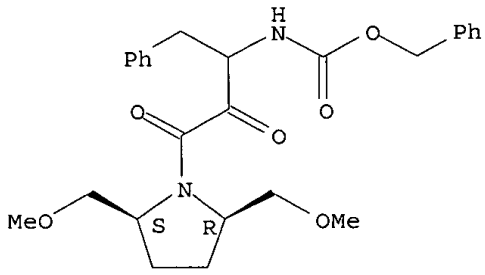
RN 191849-90-8 CAPLUS
CN Carbamic acid, [3-[3,4-dimethoxy-2,5-bis(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2R-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191850-25-6 CAPLUS
CN Carbamic acid, [3-[2,5-bis(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L18 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:938815 CAPLUS
DOCUMENT NUMBER: 124:105570
TITLE: Selectivity in the Inhibition of HIV and FIV Protease: Inhibitory and Mechanistic Studies of Pyrrolidine-Containing .alpha.-Keto Amide and

Golam Shameem

Hydroxyethylamine Core Structures

AUTHOR(S): Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.; Gustchina, Alla; Kervinen, Jukka; Zdanov, Alexander; Wlodawer, Alexander; Wong, Chi-Huey

CORPORATE SOURCE: Scripps Research Institute, La Jolla, CA, 92037, USA

SOURCE: Journal of the American Chemical Society (1995), 117(48), 11867-78
CODEN: JACSAT; ISSN: 0002-7863

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

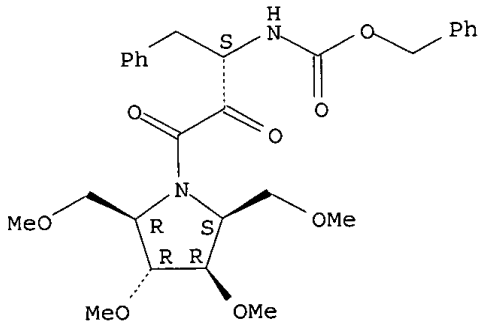
AB This study describes the development of new pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamine core structures as mechanism based inhibitors of the HIV and FIV proteases. The .alpha.-keto amide core structure is approx. 300-fold better than the corresponding hydroxyethylamine isosteric structure and 1300-fold better than the corresponding phosphinic acid deriv. as an inhibitor of the HIV protease. The .alpha.-keto amide is however not hydrated until it is bound to the HIV protease as indicated by the NMR study and the x-ray structural anal. Further anal. of the inhibition activities of hydroxyethylamine isosteres contg. modified pyrrolidine derivs. revealed that a cis-methoxy group at C-4 of the pyrrolidine would improve the binding 5- and 25-fold for the trans-isomer. Of the core structures prepd. as inhibitors of the HIV protease, none show significant inhibitory activity against the mechanistically identical FIV protease, and addnl. complementary groups are needed to improve inhibition.

IT **172696-19-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(HIV and FIV proteases inhibition by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)

RN 172696-19-4 CAPLUS

CN Carbamic acid, [3-[3,4-dimethoxy-2,5-bis(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(R*),2.alpha.,3.alpha.,4.beta.,5.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction with benzyloxycarbonyl chloride

L18 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

Golam Shameem

ACCESSION NUMBER: 1988:454505 CAPLUS
DOCUMENT NUMBER: 109:54505
TITLE: Diastereoselective reduction of .alpha.-keto amides having trans-2,5-disubstituted pyrrolidines as chiral auxiliaries
AUTHOR(S): Kawanami, Yasuhiro; Fujita, Izumi; Taniguchi, Yoshiyuki; Katsuki, Tsutomu; Yamaguchi, Masaru
CORPORATE SOURCE: Fac. Educ., Kagawa Univ., Kagawa, 760, Japan
SOURCE: Chemistry Letters (1987), (10), 2021-4
CODEN: CMLTAG; ISSN: 0366-7022
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 109:54505
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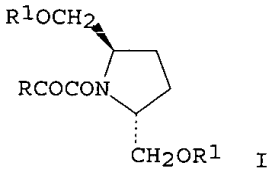
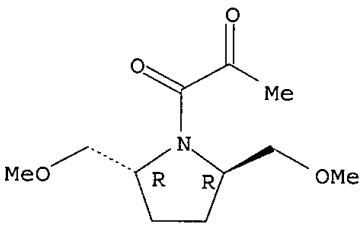


I

AB The redn. of .alpha.-keto amides I (R = Ph, Me; R1 = Me, CH2OMe) with LiBEt3H or KBEt3H proceeded with high diastereoselectivity (.ltoreq.99%) to afford the .alpha.-hydroxy amides in good yield. The effect of added crown ethers or LiBr was also examd.

IT **115378-73-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and diastereoselective redn. of)
RN 115378-73-9 CAPLUS
CN Pyrrolidine, 1-(1,2-dioxopropyl)-2,5-bis(methoxymethyl)-, (2R-trans)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> FIL REGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	14.86	699.85

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION

Golam Shameem

CA SUBSCRIBER PRICE -1.95 -13.01

FILE 'REGISTRY' ENTERED AT 14:34:27 ON 03 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 2 JAN 2003 HIGHEST RN 478001-04-6
DICTIONARY FILE UPDATES: 2 JAN 2003 HIGHEST RN 478001-04-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

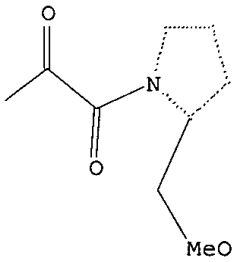
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
Uploading 09077712d.str

L19 STRUCTURE UPLOADED

=> d l19
L19 HAS NO ANSWERS
L19 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l19
SAMPLE SEARCH INITIATED 14:34:51 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 88 TO ITERATE

100.0% PROCESSED 88 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 1198 TO 2322
PROJECTED ANSWERS: 2 TO 124

Golam Shameem

L20 2 SEA SSS SAM L19

=> s l19 sss full
FULL SEARCH INITIATED 14:34:59 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 1511 TO ITERATE

100.0% PROCESSED 1511 ITERATIONS 27 ANSWERS
SEARCH TIME: 00.00.01

L21 27 SEA SSS FUL L19

=> FIL CAPLUS

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	148.15	848.00

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-13.01

FILE 'CAPLUS' ENTERED AT 14:35:02 ON 03 JAN 2003
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FILE COVERS 1907 - 3 Jan 2003 VOL 138 ISS 2
FILE LAST UPDATED: 2 Jan 2003 (20030102/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> d his

(FILE 'HOME' ENTERED AT 14:17:40 ON 03 JAN 2003)

FILE 'REGISTRY' ENTERED AT 14:17:51 ON 03 JAN 2003
L1 STRUCTURE UPLOADED
L2 3 S L1
L3 44 S L1 SSS FULL

FILE 'CAPLUS' ENTERED AT 14:18:26 ON 03 JAN 2003
L4 12 S L3
L5 11 S L4 AND HIV

Golam Shameem

```
     FILE 'REGISTRY' ENTERED AT 14:24:11 ON 03 JAN 2003
L6                STRUCTURE UPLOADED
L7             0 S L6
L8             6 S L6 SSS FULL

     FILE 'CAPLUS' ENTERED AT 14:24:48 ON 03 JAN 2003
L9             3 S L8

     FILE 'REGISTRY' ENTERED AT 14:28:43 ON 03 JAN 2003
L10               STRUCTURE UPLOADED
L11            0 S L10
L12            0 S L1O SSS FULL
L13            2 S L10 SSS FULL

     FILE 'CAPLUS' ENTERED AT 14:31:00 ON 03 JAN 2003
L14            2 S L13

     FILE 'REGISTRY' ENTERED AT 14:32:12 ON 03 JAN 2003
L15               STRUCTURE UPLOADED
L16            0 S L15
L17            4 S L15 SSS FULL

     FILE 'CAPLUS' ENTERED AT 14:32:49 ON 03 JAN 2003
L18            3 S L17

     FILE 'REGISTRY' ENTERED AT 14:34:27 ON 03 JAN 2003
L19               STRUCTURE UPLOADED
L20            2 S L19
L21           27 S L19 SSS FULL

     FILE 'CAPLUS' ENTERED AT 14:35:02 ON 03 JAN 2003

=> s l21
L22           67 L21

=> s l21/thu
             67 L21
         483001 THU/RL
L23           3 L21/THU
                  (L21 (L) THU/RL)

=> s l22 and HIV
          47189 HIV
             79 HIVS
          47196 HIV
                  (HIV OR HIVS)
L24           3 L22 AND HIV

=> s l22 and inhibitor
         399611 INHIBITOR
         421968 INHIBITORS
         649760 INHIBITOR
                  (INHIBITOR OR INHIBITORS)
L25          22 L22 AND INHIBITOR

=> s l22 and HIV(w)inhibitor?
          47189 HIV
             79 HIVS
          47196 HIV
```

Golam Shameem

```
                (HIV OR HIVS)
        804957 INHIBITOR?
           987 HIV(W)INHIBITOR?
L26          0 L22 AND HIV(W)INHIBITOR?

=> d ibib abs hitstr l23 tot

L23  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:868895  CAPLUS
DOCUMENT NUMBER:          137:369738
TITLE:                    Preparation of pyruvate derivatives for treating
                          conditions characterized by oxidative stress
INVENTOR(S):              Wang, Bing; Miller, Guy; Flaim, Stephen F.; Del Balzo,
                          Ughetta; Zhang, Wei; Janagani, Satyanarayana; Song,
                          Jingao
PATENT ASSIGNEE(S):       Galileo Laboratories, Inc., USA
SOURCE:                   PCT Int. Appl., 143 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ----------------  ----  --------       ---------------  --------
     WO 2002090314      A1   20021114       WO 2002-US14057  20020503
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
             TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                  US 2001-288649P  P  20010503
                                        US 2001-295314P  P  20010601
                                        US 2002-368456P  P  20020323
OTHER SOURCE(S):          MARPAT 137:369738
AB   Pyruvate derivs. A-X-CH2C(:W)CO-Z and A-X-CH:C(W)CO-Z [A = (un)substituted
     (cyclo)alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl,
     heterocycloalkyl, nucleoside, amino acid, di-, tri- or tetrapeptide,
     CH2COCO2R', or CH:C(OH)CO2R', where R' = H, (un)substituted (cyclo)alkyl
     or aryl; X = NR', S, SO, SO2, S-Y-S [Y = (un)substituted aryl, heteroaryl,
     nucleoside, amino acid, di, tri- or tetrapeptide], or a covalent bond to
     the sulfur atom of Cys or to the nitrogen atom of optionally substituted
     heterocyclyl; W = :O, :NORa, :NNRbRc, or N(OH)Rd, where Ra = H,
     (un)substituted alkyl, aryl, aralkyl, or alkenyl; Rb = H, (un)substituted
     (cyclo)alkyl, aryl, or aralkyl; Rc = H or (un)substituted alkyl; or RbRcN
     = 5- to 7-membered heterocyclyl; Rd = H, acyl, or (un)substituted alkyl; Z
     = OR, SR, or NRbRc, where R = (un)substituted (cyclo)alkyl, aryl, aralkyl,
     heteroaryl, heteroaralkyl, heterocyclyl, or heterocycloalkyl] or their
     pharmaceutically-acceptable salts were prepd. for treating a no. of
     conditions characterized by oxidative stress.  Certain known and novel
     pyruvate derivs. are particularly active in restoring or preserving
     metabolic integrity in oxidatively competent cells that have been
     subjected to oxygen deprivation.  Thus, 2-amino-4-[1-
     (carboxymethylcarbamoyl)-2-[2-oxo-2-(pentyloxycarbonyl)ethylsulfanyl]ethyl
     carbamoyl]butyric acid (claimed compd.) was prepd. from 3-bromopyruvic
```

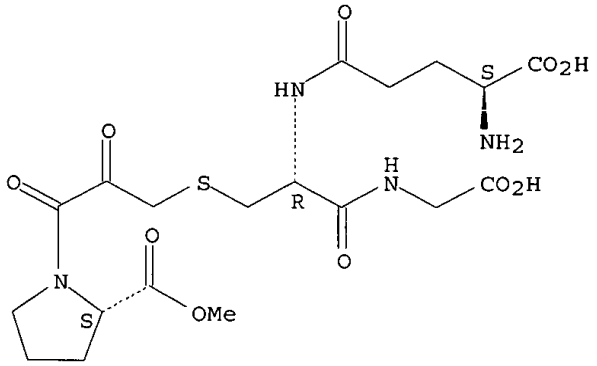
acid, pentanol, and glutathione.

IT **475294-04-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyruvate derivs., including peptide derivs., for treating conditions characterized by oxidative stress)

RN 475294-04-3 CAPLUS

CN Glycine, L-.gamma.-glutamyl-S-[3-[(2S)-2-(methoxycarbonyl)-1-pyrrolidinyl]-2,3-dioxopropyl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



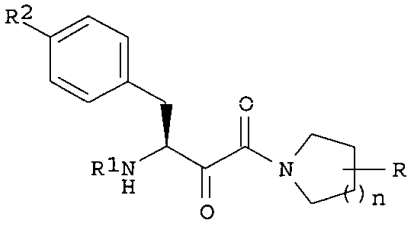
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:473732 CAPLUS
DOCUMENT NUMBER: 127:81793
TITLE: Preparation of hydroxyethylamine core structures as HIV and FIV protease inhibitors
INVENTOR(S): Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
PATENT ASSIGNEE(S): Scripps Research Institute, USA; Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
SOURCE: PCT Int. Appl., 202 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9721100	A1	19970612	WO 1996-US19571	19961209
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2238337	AA	19970612	CA 1996-2238337	19961209
AU 9712844	A1	19970627	AU 1997-12844	19961209

Golam Shameem

AU 728373 B2 20010111
EP 873519 A1 19981028 EP 1996-943657 19961209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
JP 2000502332 T2 20000229 JP 1997-521485 19961209
PRIORITY APPLN. INFO.: US 1995-568532 A2 19951207
WO 1996-US19571 W 19961209
OTHER SOURCE(S): MARPAT 127:81793
GI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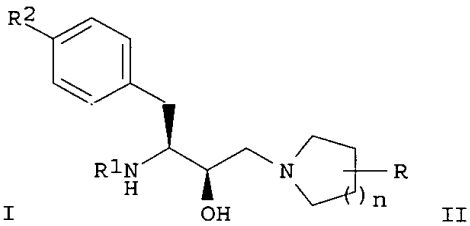
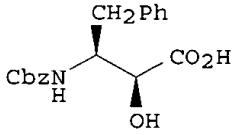
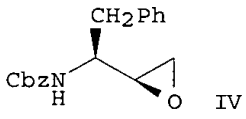

II


III


IV

AB Combinatorial libraries of HIV and FIV protease inhibitors are characterized by .alpha.-keto amide or hydroxyethylamine core structures I and II [n = 1, 2; R = one or more groups CONHCMe3, CH2OH, CH2OMe, CH2OCH2Ph, OH, OCH2Ph, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy, etc.; R1 = PhCH2O2C (Cbz), Me3CO2C (Boc), acyl; R2 = H, HO, PhCH2O, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy] flanked by on one side by substituted pyrrolidines, piperidines, or azasugars and on the other side by Phe, Tyr, or substituted tyrosines. The libraries are synthesized via coupling of the nitrogen heterocycles with hydroxy acids, e.g. III, followed by oxidn. to the keto amide, or a one-step coupling with epoxides, e.g. IV. Highly efficacious drug candidates are identified by screening the libraries for binding and inhibitory activity against both HIV and FIV protease. Drug candidates displaying clin. useful activity against both HIV and FIV protease are identified as being potentially resistive against a loss of inhibitory activity due to development of resistant strains of HIV.

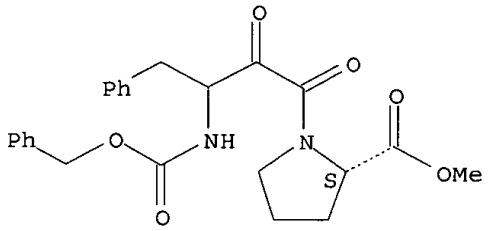
IT **191849-88-4P 191849-90-8P 191849-95-3P**
191850-25-6P 191850-26-7P 191850-35-8P
191850-61-0P 191850-93-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of hydroxyethylamine core structures as HIV and FIV protease inhibitors)

RN 191849-88-4 CAPLUS

CN L-Proline, 1-[1,2-dioxo-4-phenyl-3-[[(phenylmethoxy)carbonyl]amino]butyl]-

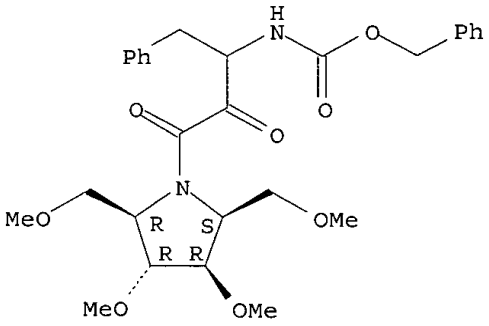
, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



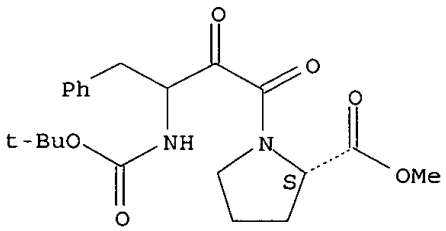
RN 191849-90-8 CAPLUS
CN Carbamic acid, [3-[3,4-dimethoxy-2,5-bis(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2R-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



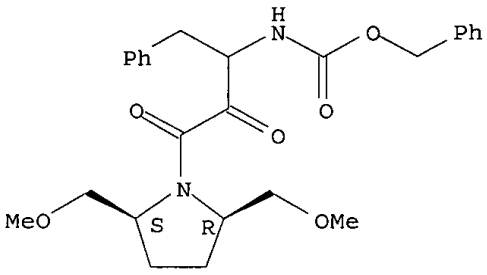
RN 191849-95-3 CAPLUS
CN L-Proline, 1-[3-[[(1,1-dimethylethoxy)carbonyl]amino]-1,2-dioxo-4-phenylbutyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



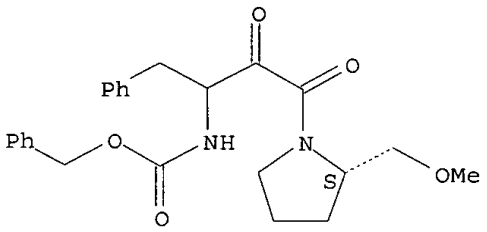
RN 191850-25-6 CAPLUS
CN Carbamic acid, [3-[2,5-bis(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



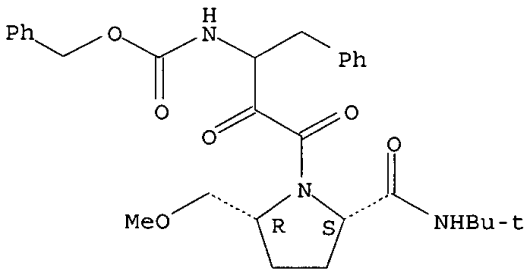
RN 191850-26-7 CAPLUS
CN Carbamic acid, [3-[2-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191850-35-8 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

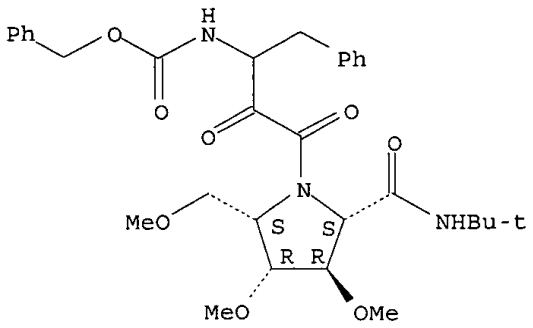
Absolute stereochemistry.



RN 191850-61-0 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-dimethoxy-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

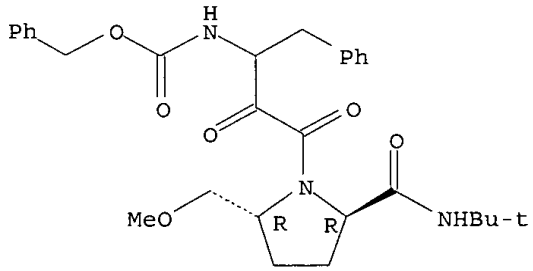
Absolute stereochemistry.

Golam Shameem



RN 191850-93-8 CAPLUS
CN Carbamic acid, [3 [2 [[(1,1 dimethylethyl)amino]carbonyl]-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2R-(2.alpha.,5.beta.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



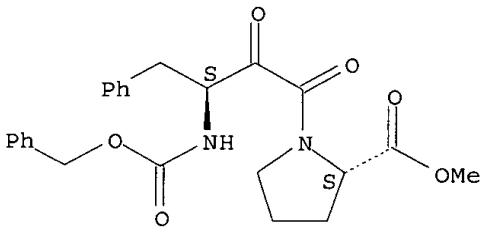
L23 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:938815 CAPLUS
DOCUMENT NUMBER: 124:105570
TITLE: Selectivity in the Inhibition of HIV and FIV Protease: Inhibitory and Mechanistic Studies of Pyrrolidine-Containing .alpha.-Keto Amide and Hydroxyethylamine Core Structures
AUTHOR(S): Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.; Gustchina, Alla; Kervinen, Jukka; Zdanov, Alexander; Wlodawer, Alexander; Wong, Chi-Huey
CORPORATE SOURCE: Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1995), 117(48), 11867-78
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study describes the development of new pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamine core structures as mechanism based inhibitors of the HIV and FIV proteases. The .alpha.-keto amide core structure is approx. 300-fold better than the corresponding hydroxyethylamine isosteric structure and 1300-fold better than the

corresponding phosphinic acid deriv. as an inhibitor of the HIV protease. The .alpha.-keto amide is however not hydrated until it is bound to the HIV protease as indicated by the NMR study and the x-ray structural anal. Further anal. of the inhibition activities of hydroxyethylamine isosteres contg. modified pyrrolidine derivs. revealed that a cis-methoxy group at C-4 of the pyrrolidine would improve the binding 5- and 25-fold for the trans-isomer. Of the core structures prepd. as inhibitors of the HIV protease, none show significant inhibitory activity against the mechanistically identical FIV protease, and addnl. complementary groups are needed to improve inhibition.

IT **172696-13-8P 172696-19-4P 172696-30-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(HIV and FIV proteases inhibition by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)

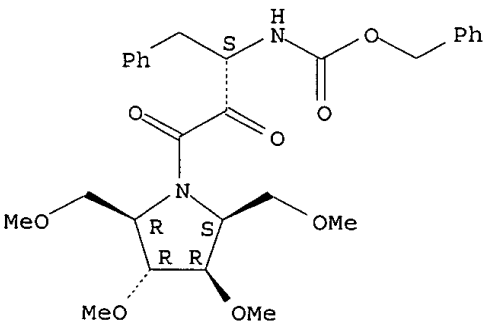
RN 172696-13-8 CAPLUS
CN L-Proline, 1-[(3S)-1,2-dioxo-4-phenyl-3-[[(phenylmethoxy)carbonyl]amino]butyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172696-19-4 CAPLUS
CN Carbamic acid, [3-[3,4-dimethoxy-2,5-bis(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(R*),2.alpha.,3.alpha.,4.beta.,5.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172696-30-9 CAPLUS
CN L-Proline, 1-[1,2-dioxo-4-phenyl-3-[[(phenylmethoxy)carbonyl]amino]butyl]-, methyl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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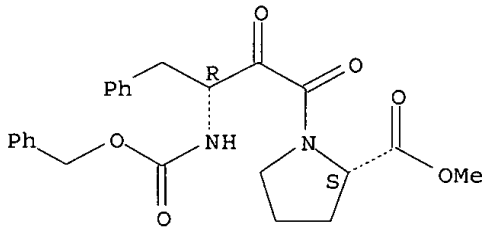
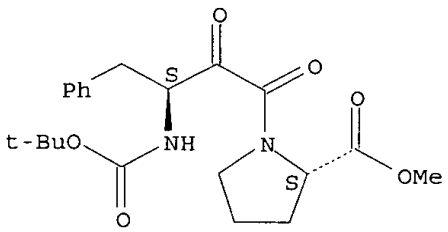


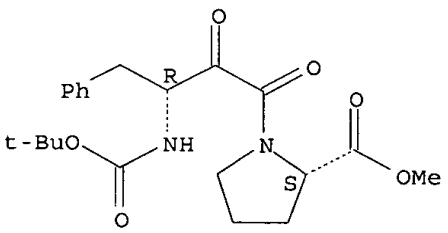
IT **161723-79-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(HIV and FIV proteases inhibition by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)
RN 161723-79-1 CAPLUS
CN L-Proline, 1-[3-[[(1,1-dimethylethoxy)carbonyl]amino]-1,2-dioxo-4-phenylbutyl]-, methyl ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **161723-78-0P 172696-19-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction with benzyloxycarbonyl chloride)
RN 161723-78-0 CAPLUS
CN L-Proline, 1-[(3R)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-1,2-dioxo-4-phenylbutyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

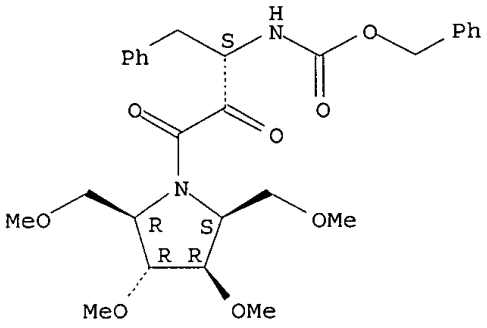


RN 172696-19-4 CAPLUS
CN Carbamic acid, [3-[3,4-dimethoxy-2,5-bis(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester,

Golam Shameem

[2S-[1(R*),2.alpha.,3.alpha.,4.beta.,5.alpha.]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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L24 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:473732 CAPLUS
DOCUMENT NUMBER: 127:81793
TITLE: Preparation of hydroxyethylamine core structures as **HIV** and FIV protease inhibitors
INVENTOR(S): Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
PATENT ASSIGNEE(S): Scripps Research Institute, USA; Wong, Chi-Huey; Slee, Deborah H.; Laslo, Karen
SOURCE: PCT Int. Appl., 202 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9721100	A1	19970612	WO 1996-US19571	19961209
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2238337	AA	19970612	CA 1996-2238337	19961209
AU 9712844	A1	19970627	AU 1997-12844	19961209
AU 728373	B2	20010111		
EP 873519	A1	19981028	EP 1996-943657	19961209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2000502332	T2	20000229	JP 1997-521485	19961209

PRIORITY APPLN. INFO.: US 1995-568532 A2 19951207
WO 1996-US19571 W 19961209
OTHER SOURCE(S): MARPAT 127:81793
GI

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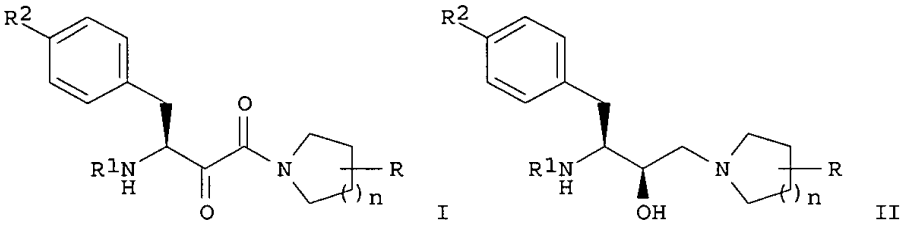
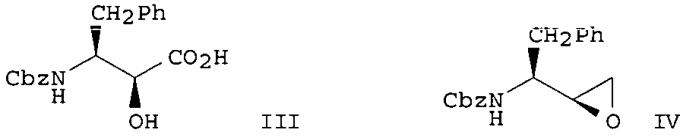


I II



III IV

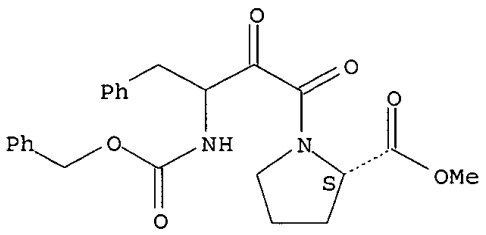
AB Combinatorial libraries of **HIV** and FIV protease inhibitors are characterized by .alpha.-keto amide or hydroxyethylamine core structures I and II [n = 1, 2; R = one or more groups CONHCMe3, CH2OH, CH2OMe, CH2OCH2Ph, OH, OCH2Ph, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy, etc.; R1 = PhCH2O2C (Cbz), Me3CO2C (Boc), acyl; R2 = H, HO, PhCH2O, C1-4 alkoxy, optionally nitro-substituted 2-, 3-, or 4-MeOC6H4CH2O, 2,3- or 3,4-methylenedioxyphenylmethoxy] flanked by on one side by substituted pyrrolidines, piperidines, or azasugars and on the other side by Phe, Tyr, or substituted tyrosines. The libraries are synthesized via coupling of the nitrogen heterocycles with hydroxy acids, e.g. III, followed by oxidn. to the keto amide, or a one-step coupling with epoxides, e.g. IV. Highly efficacious drug candidates are identified by screening the libraries for binding and inhibitory activity against both **HIV** and FIV protease. Drug candidates displaying clin. useful activity against both **HIV** and FIV protease are identified as being potentially resistive against a loss of inhibitory activity due to development of resistant strains of **HIV**.

IT **191849-88-4P 191849-90-8P 191849-95-3P**
191850-25-6P 191850-26-7P 191850-35-8P
191850-61-0P 191850-93-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of hydroxyethylamine core structures as **HIV** and FIV protease inhibitors)

RN 191849-88-4 CAPLUS

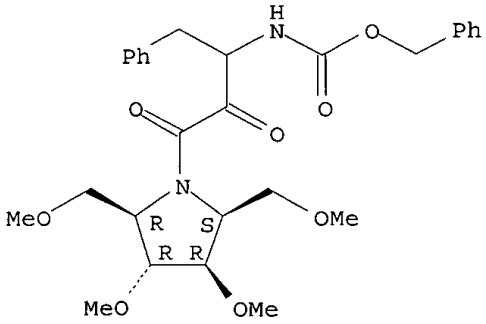
CN L-Proline, 1-[1,2-dioxo-4-phenyl-3-[[(phenylmethoxy)carbonyl]amino]butyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



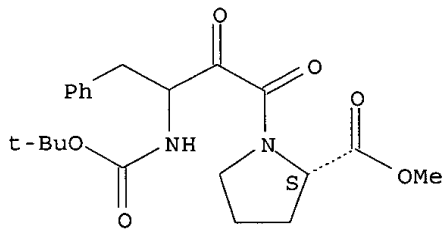
RN 191849-90-8 CAPLUS
CN Carbamic acid, [3-[3,4-dimethoxy-2,5-bis(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2R-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191849-95-3 CAPLUS
CN L-Proline, 1-[3-[[(1,1-dimethylethoxy)carbonyl]amino]-1,2-dioxo-4-phenylbutyl]-, methyl ester (9CI) (CA INDEX NAME)

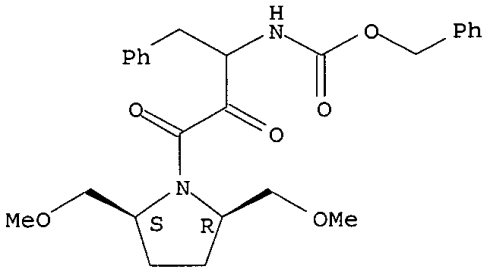
Absolute stereochemistry.



RN 191850-25-6 CAPLUS
CN Carbamic acid, [3-[2,5-bis(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

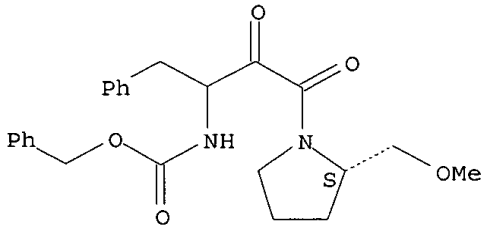
Absolute stereochemistry.

Golam Shameem



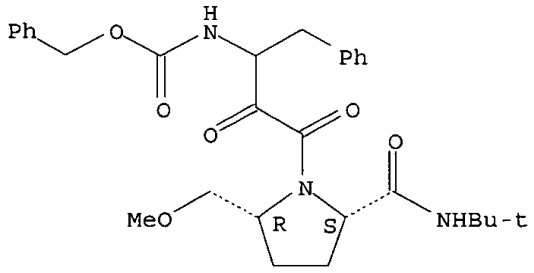
RN 191850-26-7 CAPLUS
CN Carbamic acid, [3-[2-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191850-35-8 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

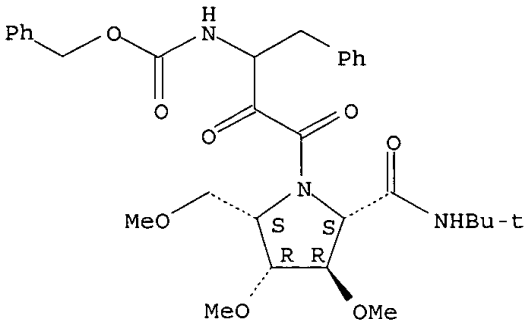
Absolute stereochemistry.



RN 191850-61-0 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-3,4-dimethoxy-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-(2.alpha.,3.beta.,4.alpha.,5.alpha.)]-[partial]- (9CI) (CA INDEX NAME)

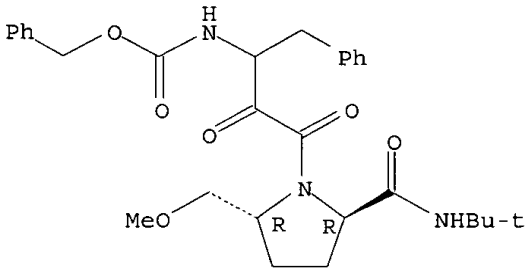
Absolute stereochemistry.

Golam Shameem



RN 191850-93-8 CAPLUS
CN Carbamic acid, [3-[2-[[(1,1-dimethylethyl)amino]carbonyl]-5-(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2R-(2.alpha.,5.beta.)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L24 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:938815 CAPLUS
DOCUMENT NUMBER: 124:105570
TITLE: Selectivity in the Inhibition of **HIV** and FIV Protease: Inhibitory and Mechanistic Studies of Pyrrolidine-Containing .alpha.-Keto Amide and Hydroxyethylamine Core Structures
AUTHOR(S): Slee, Deborah H.; Laslo, Karen L.; Elder, John H.; Ollmann, Ian R.; Gustchina, Alla; Kervinen, Jukka; Zdanov, Alexander; Wlodawer, Alexander; Wong, Chi-Huey
CORPORATE SOURCE: Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1995), 117(48), 11867-78
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study describes the development of new pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamine core structures as mechanism based inhibitors of the **HIV** and FIV proteases. The .alpha.-keto amide core structure is approx. 300-fold better than the corresponding hydroxyethylamine isosteric structure and 1300-fold better than the corresponding phosphinic acid deriv. as an inhibitor of the **HIV**

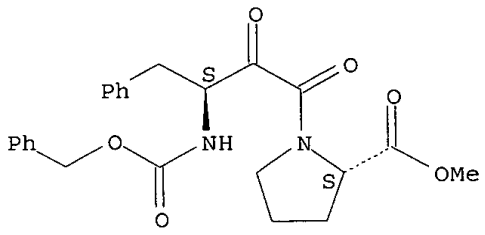
Golam Shameem

protease. The .alpha.-keto amide is however not hydrated until it is bound to the **HIV** protease as indicated by the NMR study and the x-ray structural anal. Further anal. of the inhibition activities of hydroxyethylamine isosteres contg. modified pyrrolidine derivs. revealed that a cis-methoxy group at C-4 of the pyrrolidine would improve the binding 5- and 25-fold for the trans-isomer. Of the core structures prepd. as inhibitors of the **HIV** protease, none show significant inhibitory activity against the mechanistically identical FIV protease, and addnl. complementary groups are needed to improve inhibition.

IT **172696-13-8P 172696-19-4P 172696-30-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**HIV** and FIV proteases inhibition by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)

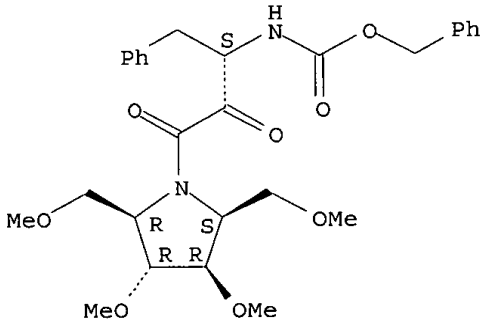
RN 172696-13-8 CAPLUS
CN L-Proline, 1-[(3S)-1,2-dioxo-4-phenyl-3-[[(phenylmethoxy)carbonyl]amino]butyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 172696-19-4 CAPLUS
CN Carbamic acid, [3-[3,4-dimethoxy-2,5-bis(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(R*),2.alpha.,3.alpha.,4.beta.,5.alpha.]]- (9CI) (CA INDEX NAME)

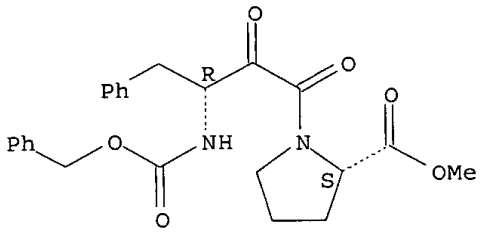
Absolute stereochemistry.



RN 172696-30-9 CAPLUS
CN L-Proline, 1-[1,2-dioxo-4-phenyl-3-[[(phenylmethoxy)carbonyl]amino]butyl]-, methyl ester, (R)- (9CI) (CA INDEX NAME)

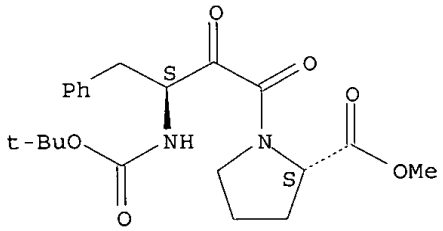
Absolute stereochemistry.

Golam Shameem



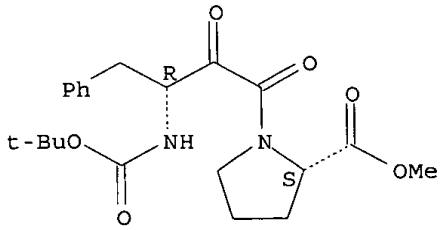
IT **161723-79-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**HIV** and FIV proteases inhibition by pyrrolidine-contg. .alpha.-keto amide and hydroxyethylamines)
RN 161723-79-1 CAPLUS
CN L-Proline, 1-[3-[[(1,1-dimethylethoxy)carbonyl]amino]-1,2-dioxo-4-phenylbutyl]-, methyl ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **161723-78-0P 172696-19-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction with benzyloxycarbonyl chloride)
RN 161723-78-0 CAPLUS
CN L-Proline, 1-[(3R)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-1,2-dioxo-4-phenylbutyl]-, methyl ester (9CI) (CA INDEX NAME)

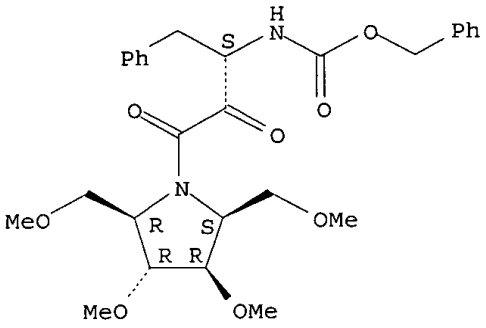
Absolute stereochemistry.



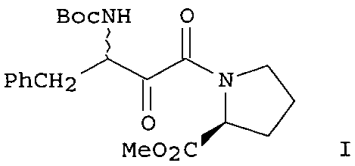
RN 172696-19-4 CAPLUS
CN Carbamic acid, [3-[3,4-dimethoxy-2,5-bis(methoxymethyl)-1-pyrrolidinyl]-2,3-dioxo-1-(phenylmethyl)propyl]-, phenylmethyl ester, [2S-[1(R*),2.alpha.,3.alpha.,4.beta.,5.alpha.]]- (9CI) (CA INDEX NAME)

Golam Shameem

Absolute stereochemistry.



L24 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:338480 CAPLUS
DOCUMENT NUMBER: 122:188156
TITLE: .alpha.-Ketoamide Phe-Pro isostere as a new core structure for the inhibition of **HIV** protease
AUTHOR(S): Munoz, Benito; Giam, Chou-Zen; Wong, Chi-Huey
CORPORATE SOURCE: Dep. Chem., Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE: Bioorganic & Medicinal Chemistry (1994), 2(10), 1085-90
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

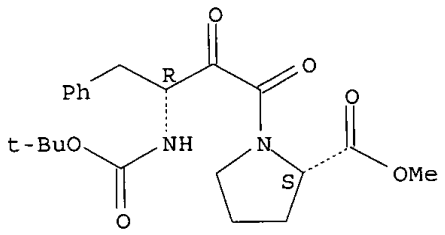
AB Studies on the inhibition of **HIV**-1 protease utilizing a core isostere with replacement of the scissile bond for an .alpha.-amino-ketone have resulted in the development of an .alpha.-keto-amide isosteric replacement of the Phe-Pro scissile amide bond. The simple dipeptide isostere I was a promising new core structure for the development of the enzyme inhibitors. I exhibited Ki = 6 .mu.M against **HIV**-1 protease, compared to 230 .mu.M and >50 .mu.M for the corresponding phosphinic acid and hydroxyethylamine isosteres.

IT **161723-78-0P 161723-79-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of a phenylalanylproline ketoamide isostere as a new **HIV** protease inhibitor)
RN 161723-78-0 CAPLUS

Golam Shameem

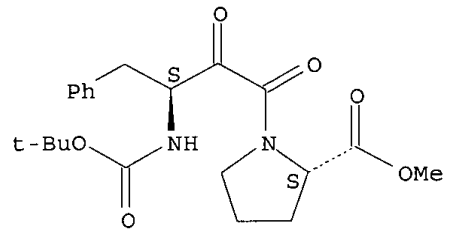
CN L-Proline, 1-[(3R)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-1,2-dioxo-4-phenylbutyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 161723-79-1 CAPLUS
CN L-Proline, 1-[3-[[(1,1-dimethylethoxy)carbonyl]amino]-1,2-dioxo-4-phenylbutyl]-, methyl ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	37.91	885.91
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.91	-16.92

STN INTERNATIONAL LOGOFF AT 14:38:18 ON 03 JAN 2003